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THE NEPHROTIC SYNDROME IN CHILDREN TREATED WITH A.C.T.H. AND CORTISONE*

BY

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From the Children's Memorial Hospital, Montreal, and the Department of Pediatrics, McGill University, Montreal

(RECEIVED FOR PUBLICATION DECEMBER 28, 1951)

The purpose of this communication is to report seven cases of the nephrotic syndrome in children treated with cortisone and adrenocorticotropic hormone (A.C.T.H.) during the past 15 months. All seven children in this series, with one exception, were males, their ages ranging from 3 to 12 years. In only one child did the disease follow an acute infection. In one other child the syndrome appeared after a skin burn. Marked haematuria was not present at the onset in any case, but in five of the patients red cells were found in the urine on admission and from time to time. Oedema, ascites, oliguria and anorexia were present in all. In one child (Case 1) there was an increase in blood pressure, and in three children (Cases 1, 4 and 7) elevation of the blood non-protein nitrogen (N.P.N.). Serum cholesterol values and erythrocyte sedimentation rates were high in all seven patients, and serum proteins were low, with depression of the albumin fraction to 2 g. or less per 100 ml. of serum. In all children the urine showed gross albuminuria and hyaline and granular casts.

The duration of the disease before treatment varied. In the first patient there was a six-month history; in patients 2 and 7, a 21-month and a 30-month history respectively. Patients 5 and 6 had been ill for two to three months, while in patients 3 and 4 the disease had been present for one week only.

Plan of Study

The children were in hospital for periods varying from one to five months, and were in bed during the entire period of study. They were weighed daily before breakfast, and blood pressure and temperature readings were recorded at least twice daily. The total fluid intake was measured. Blood was drawn weekly for biochemical examination and sedimentation rates in the first four patients, and twice weekly in the remainder. Eosinophil counts were done every two days in the early cases, twice weekly in the later cases. Total white blood counts, differential counts and haemoglobin determinations were followed at frequent intervals.

Complete 24-hour urine collections were attempted in all patients. These were successfully carried out in four of the children who were maintained on diets containing not more than 35 mEq of sodium daily. One child was placed on a diet of known caloric and nitrogen content. Urine determinations included 24-hour excretions of protein, sodium, chloride and water in three patients, and of water, protein, chloride, nitrogen and creatinine in one patient. The urinary excretion of formaldehydogenic steroids was measured from time to time in two patients (Cases 5 and 6).

Cortisone acetate was injected intramuscularly once daily, and was given for a period of 10 days. The total dose varied from 600 to 1,500 mg. A.C.T.H. (Armour) was given by intramuscular injection at six-hourly intervals, for periods varying between four days and five weeks. The dose varied from 40 mg. to 100 mg. daily, and the preparation used was equivalent to the LA-1-A standard.

Methods of Investigation

Blood chemical studies were made on venous blood before therapy was started and subsequently at weekly or twice-weekly intervals. All colorimetric determinations were made on an Evelyn photoelectric colorimeter. Protein was determined by micro-Kjeldahl digestion followed by Nesslerization (Kolmer and Boerner, 1945). Albumin was determined after precipitation of the globulins with 22·3% sodium sulphate and ether, and globulins by difference (Kingsley, 1942). Sodium was determined colorimetrically as the zinc uranyl acetate

* These investigations were supported by a grant from the National Research Council of Canada who also supplied the A.C.T.H. and cortisone used in this study.

complex (Albanese and Lein, 1948), and chlorides either by the Volhard procedure (Peters and Van Slyke, 1932) or by the method of Schales and Schales (1941). Total cholesterol was determined by the Liebermann-Burchard reaction (Kolmer and Boerner, 1945) and sugar by the method of Folin and Wu (1920). Urine protein was determined after precipitation with 10% trichloracetic acid, urine creatinine by Folin's (Kolmer and Boerner, 1945) method. Urinary corticoids were determined on the total lipid fraction of the urine by the Venning modification (personal communication) of the method of Daughaday, Jaffe and Williams (1948).

Haematological studies were done on capillary blood twice weekly and standard techniques were followed. Sedimentation rates were performed by the method of Wintrobe. Eosinophils were counted frequently during the first few days of therapy and twice weekly subsequently, by the method of Randolph (1949). A nitrogen balance study was carried out on one patient old enough to have adequate bowel and bladder control. The dietary content of nitrogen and calories was fairly constant and was calculated from standard food tables (Sherman, 1946), the diets themselves being similar to those of Macy (1942). Urine nitrogen and creatinine were determined on daily urine specimens collected from 8 a.m. to 8 a.m. The faecal output of nitrogen was not measured but was assumed to be more or less constant.

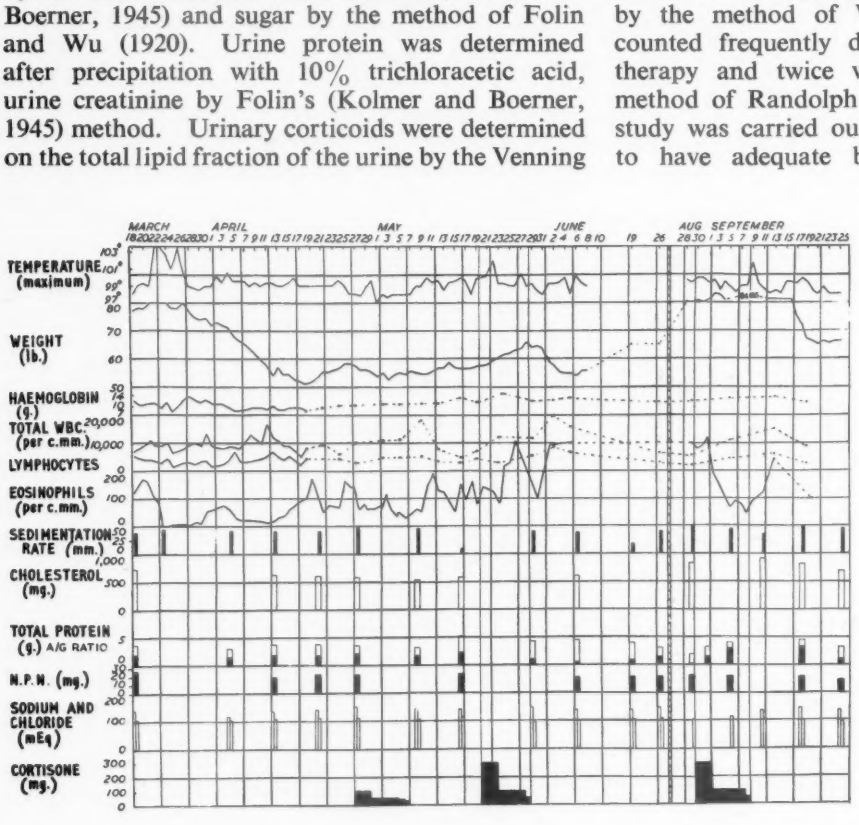

FIG. 1 (top)

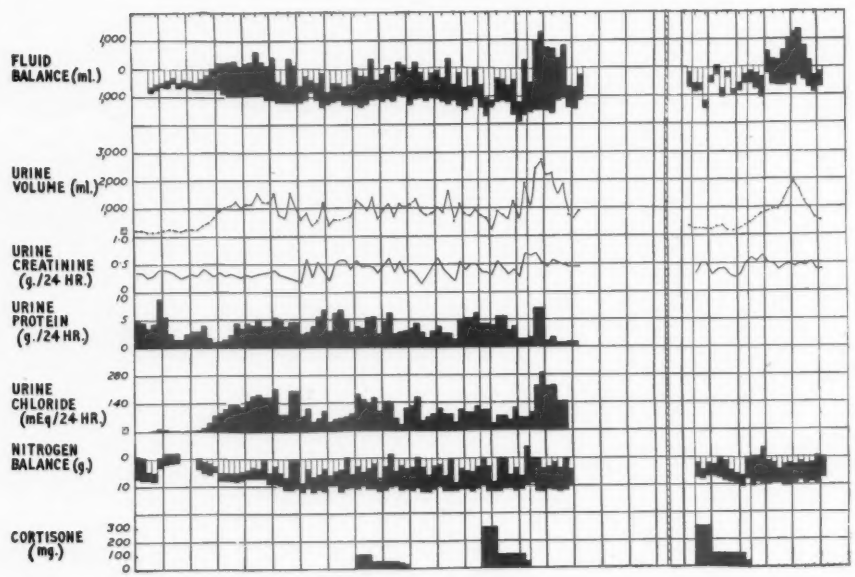

FIG. 2 (bottom)

Case Reports

Case 1. S.S., a 6-year-old white boy, was first admitted to hospital in December, 1949. His illness had begun suddenly two months before with oedema and abnormal urinary findings of red blood cells, white blood cells, hyaline and granular casts, and 2,000 mg. of albumin per 100 ml. The blood pressure was 120/90. The N.P.N. was found to be 51 mg., serum cholesterol 425 mg., total serum protein 3·2 g., albumin 1·8 g. and globulin 1·4 g. per 100 ml. On re-admission in March, 1950, the picture was essentially the same, and at that time the urea clearance was 89% of normal. On March 22, while under preliminary observation, he developed pneumonia. This was followed eight days later by a profuse diuresis and a loss of 25 lb. in weight (Figs. 1 and 2).

By April some oedema had recurred and he received 600 mg. of cortisone over

a 10-day period. Except for a moderate drop in eosinophils and a loss of 2 lb. in weight, the treatment was ineffective (Fig. 1). On May 20 a second course of cortisone was begun, 1,450 mg. being administered in nine days. During treatment the weight increased, the blood pressure rose and eosinophils rose after a slight fall. On the last day of therapy diuresis began and was associated with a high output of chlorides (Fig. 2). Albuminuria decreased and the serum albumin level rose. For one month he remained free of oedema and had an excellent appetite. He then reverted to his previous condition. On his third admission in August, 1950, he was again very oedematous, and was given 1,500 mg. of cortisone over 10 days. Diuresis began four days after withdrawal of the hormone. The patient lost 18 lb. in weight, but on this occasion some oedema remained.

FOLLOW-UP. Oedema recurred, and in a short time he received a fourth course of cortisone to which he did not respond. He again became oedema-free a month or two later following severe cellulitis. He remained relatively well during the winter, but in June, 1951, was in renal failure with many red cells in the urine, haemoglobin of 4 g. %, a non-protein nitrogen level of 150 mg. and a creatinine level of 10 mg. per 100 ml. of blood. The patient died 20 months after the onset of symptoms. At necropsy the kidneys were moderately overweight with a finely granular surface. There was slight cardiomegaly and evidence of left myocardial hypertrophy. Microscopically the kidneys showed a moderate degree of collapse fibrosis with moderately extensive atrophy of the secretory kidney tubules. The glomeruli were reduced in number. The remainder showed scarring and occasional crescent formation. The normal glomeruli and tubules showed hypertrophy and dilatation. There was a mild interstitial nephritis, focal in character. The arteries and arterioles were normal. The picture was that of early chronic (third stage) glomerulonephritis.

Case 2. M.P., a 3½-year-old white boy, was admitted on March 21, 1950, with a history of having developed generalized oedema a few days following severe scalding of one arm two years previously. He had had numerous spontaneous diureses, and also a diuresis following measles to which he was intentionally exposed. On admission there was marked oedema, ascites and unilateral hydrothorax, but no hypertension. The urine showed 100 mg. of albumin per 100 ml., moderate numbers of red cells, white cells and casts. Biochemical values of the serum were as follows: cholesterol 1,239 mg., non-protein nitrogen 37 mg., total protein 3·7 g., albumin 1·49 g. and globulin 2·21 g.

While under observation he developed two rather severe upper respiratory infections, each accompanied by a fall in circulating eosinophils to zero (Fig. 3). Neither of these infections was followed by diuresis. He was then given cortisone in doses of 100 mg. for three days, followed by 50 mg. for six days. Eosinophils fell to zero on the fifth day, and there was a slight increase in serum albumin concentration during therapy, but no other response. Urea clearance at this time was 56% of normal.

Throughout his hospital stay he showed poor response to antibiotics, and eventually died of pneumonia and otitis media. At necropsy the kidneys were slightly overweight and pale, but otherwise grossly normal. Microscopically there was slight focal tubular atrophy and collapse fibrosis, with focal areas of tubular dilatation without inflammation. The reduction in the number of glomeruli was slight. The glomeruli all showed varying degrees of basement membrane thickening and the changes corresponded to those described by Bell (1946) under the term membraneous glomerulonephritis. Proliferative changes were absent.

Case 3. C.A., a 3½-year-old white boy, had been ill for only one week with slight fever, oliguria and rapidly

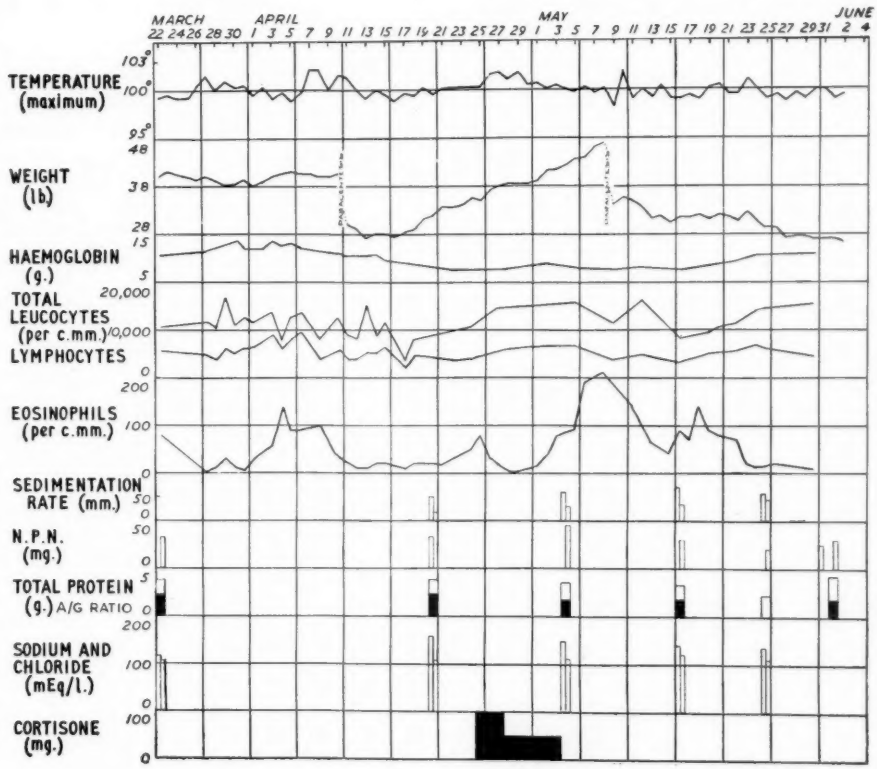

FIG. 3

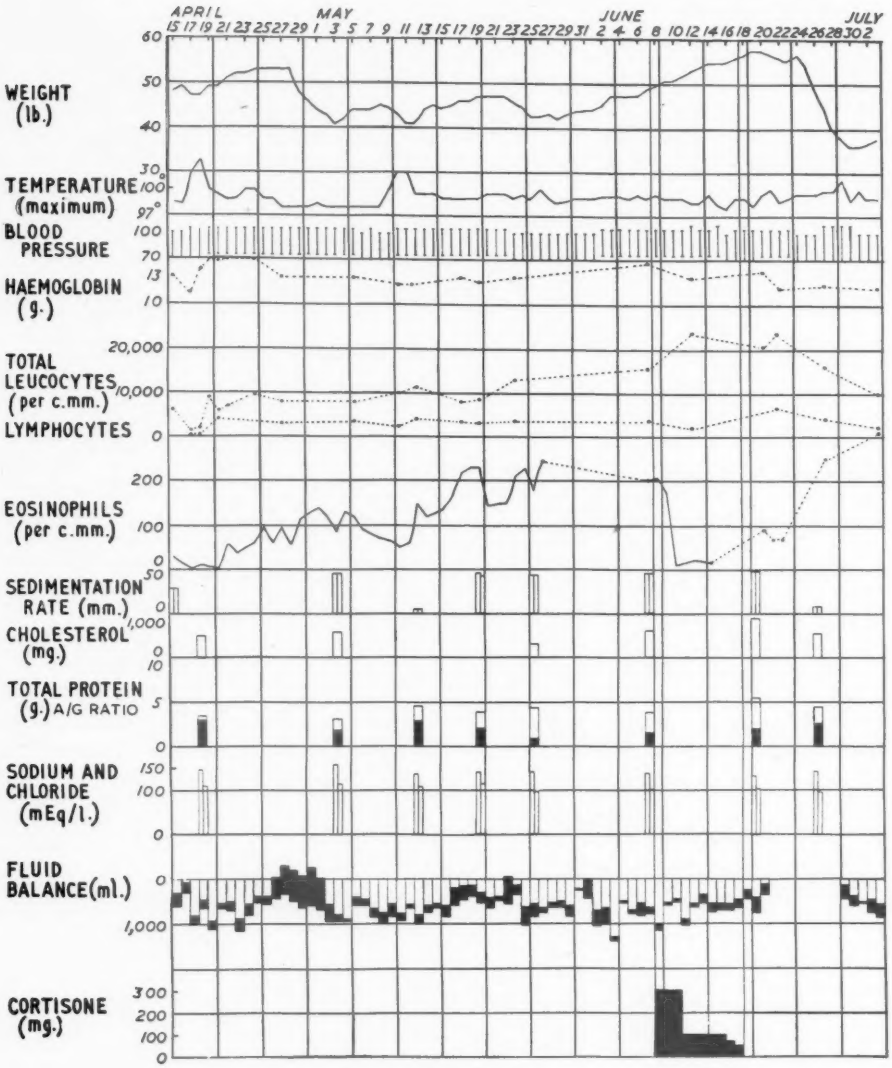

FIG. 4

developing oedema and ascites before admission to hospital. On examination there were no abnormal physical findings besides anasarca. The urine contained 500 mg. of albumin per 100 ml., numerous casts, but no red cells. Serum albumin measured 0·99 g., globulin 2·47 g., cholesterol 550 mg. and non-protein nitrogen 27 mg. The sedimentation rate was 27 mm. in the hour.

On April 18, 1950, shortly after admission, the patient developed pneumonia which was accompanied by a low total white count and a fall in eosinophils to zero (Fig. 4). He was treated with aureomycin. For nine days after the onset of infection he showed marked oliguria and continued to gain weight. As the eosinophils reappeared in the circulating blood, the total white count rose. Nine days after the onset diuresis began. The loss of fluid lasted for six days, and resulted in partial loss of oedema. A second febrile episode on May 10 was followed by slighter diuresis 10 days later, at the end of which serum albumin and cholesterol were within normal limits.

Oedema recurred almost immediately, while serum cholesterol began to rise and serum albumin to decline. The sedimentation rate remained high.

In June, 1,525 mg. of cortisone were given over a 10-day period, during which time the values for serum albumin and cholesterol rose sharply. Diuresis occurred eight days after hormone withdrawal, and resulted in complete loss of oedema, and the return of the sedimentation rate to normal. The child was then discharged.

FOLLOW-UP. Three months after therapy, abnormal blood chemical findings were again present. The sedimentation rate was 45 mm., and massive albuminuria and mild pitting oedema of the feet had recurred. Five months after therapy, however, there was no oedema, biochemical abnormality or albuminuria. Over the ensuing 11 months short bouts of oedema recurred several times. The urine on occasion has contained albumin, but at other times has been free of protein. At no time during the 16 months following his one course of cortisone has the child's condition warranted re-admission to hospital.

Case 4. S.F., a 4-year-old boy, was well until one week before entering hospital when he developed fever and oliguria. Oedema developed rapidly and was extreme by June 21, 1950, the date of admission. Albuminuria, hypercholesterolaemia and hypoalbuminaemia were present. The non-protein nitrogen was 54 mg., the blood pressure normal and no red cells were found in the urine. A bacterial pneumonia developed soon after admission and abdominal paracentesis was done for relief of distention. On the following day, June 23, cortisone was started; the child received 800 mg. in eight days. The child continued to lose weight throughout the period of therapy, due partly to drainage from the paracentesis wound, partly to a mild diuresis which may have resulted from the

pneumonia. After treatment was stopped there was an increased urinary output for three days, though some oedema remained. The sedimentation rate and the serum cholesterol concentration both fell progressively, and serum albumin showed a marked, but not sustained, rise (Fig. 5). Urea clearance at this time was 76% of normal.

A second course of cortisone was begun 16 days after the end of the first; the total dose this time was increased to 1,500 mg. Urinary output increased during the latter half of therapy, but marked diuresis and weight loss were delayed until the fifth day following the end of treatment. The serum albumin increased during therapy and showed a further increase after cessation. The cholesterol level rapidly fell to normal and the sedimentation rate remained low. Albumin did not disappear from the urine, but was reduced in amount.

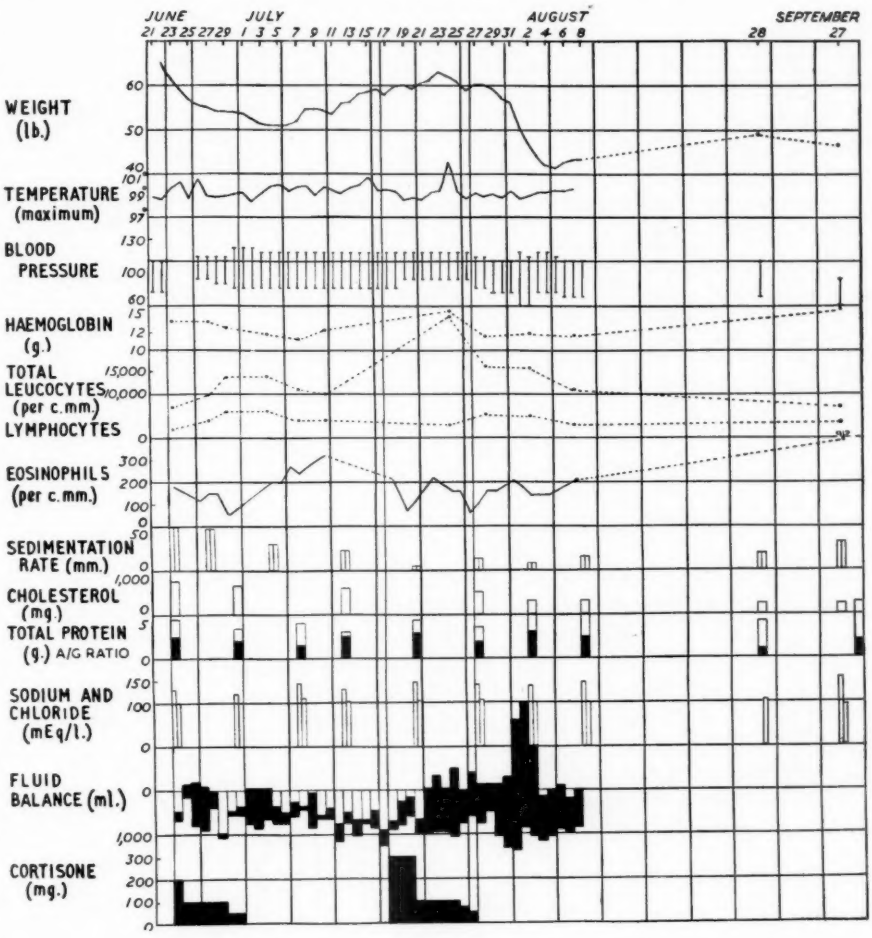

FIG. 5

FOLLOW-UP. Two months following the second course of therapy there had been no recurrence of oedema, serum albumin was still somewhat low and the urine contained 300 mg. % of albumin. The serum biochemical values gradually returned to normal, and albumin disappeared from the urine for a time, but was again present in small amounts 10 months after discharge. Very mild oedema reappeared in the eighth month following therapy, and again in the twelfth month. These bouts of oedema were accompanied by proteinuria. The child otherwise has remained well and active.

Case 5. P.W., a 2½-year-old girl, was never entirely well following severe pharyngitis in July, 1950. Oedema appeared two months later, beginning in the feet, and she was admitted to another hospital with anasarca, proteinuria, an elevated sedimentation rate and the following serum biochemical findings: non-protein nitrogen 37·6 mg., cholesterol 349 mg., total protein 4·8 g., albumin 0·4 g. and globulin 4·4 g. per 100 ml. In October, 1950, she was transferred to this hospital for treatment with A.C.T.H. and received 10 mg. every six hours for four days, when hormone therapy was stopped because of fever and abdominal pain. Diuresis began 24 hours later, and after 10 days all oedema had been discharged (Fig. 6).

During diuresis proteinuria decreased progressively and the urine was free of albumin for three days. Albumin then reappeared in small amounts which gradually increased until 3 to 4 g. per 100 ml. were again being excreted. The transitory disappearance of protein from the urine after a short course of A.C.T.H. suggested the possibility that a longer course might result in a more prolonged remission of proteinuria, and possibly prevent the reaccumulation of oedema. A.C.T.H. was accordingly administered again in November, this time for 40 days.

There was a rapid decrease in albumin excretion during therapy (Fig. 7), the amount of protein lost decreasing from 0·95 g. to 0·15 g. daily. Improvement continued after therapy was discontinued, but albumin never entirely disappeared from the urine. Oedema disappeared a day or two after therapy was begun and did not return. Urinary sodium excretion remained normal, varying between 20 and 30 mEq daily. The patient's ability to excrete sodium was demonstrated by the rapid elimination of a test dose of salt on January 27, just before discharge. It was of interest that the elimination of the increased amount of sodium

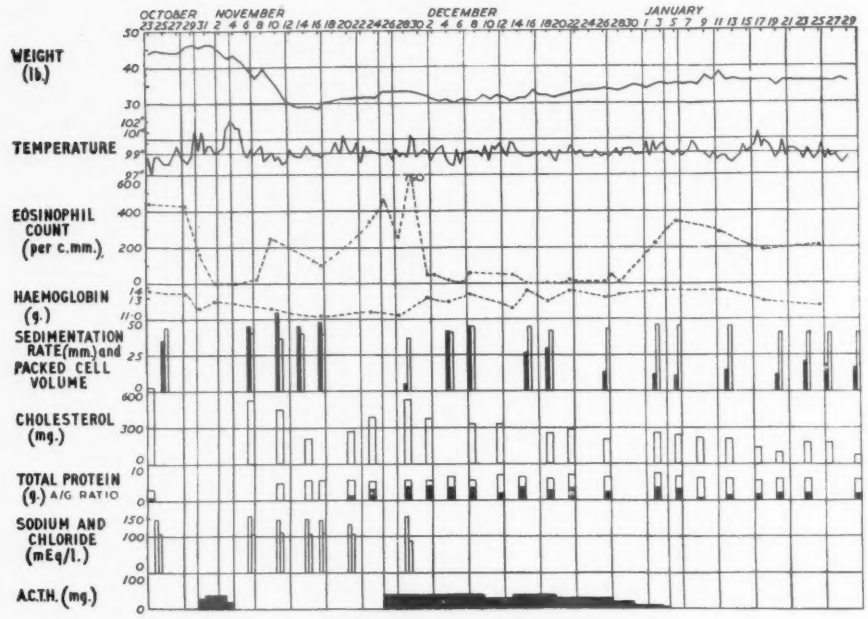

FIG. 6 (top)

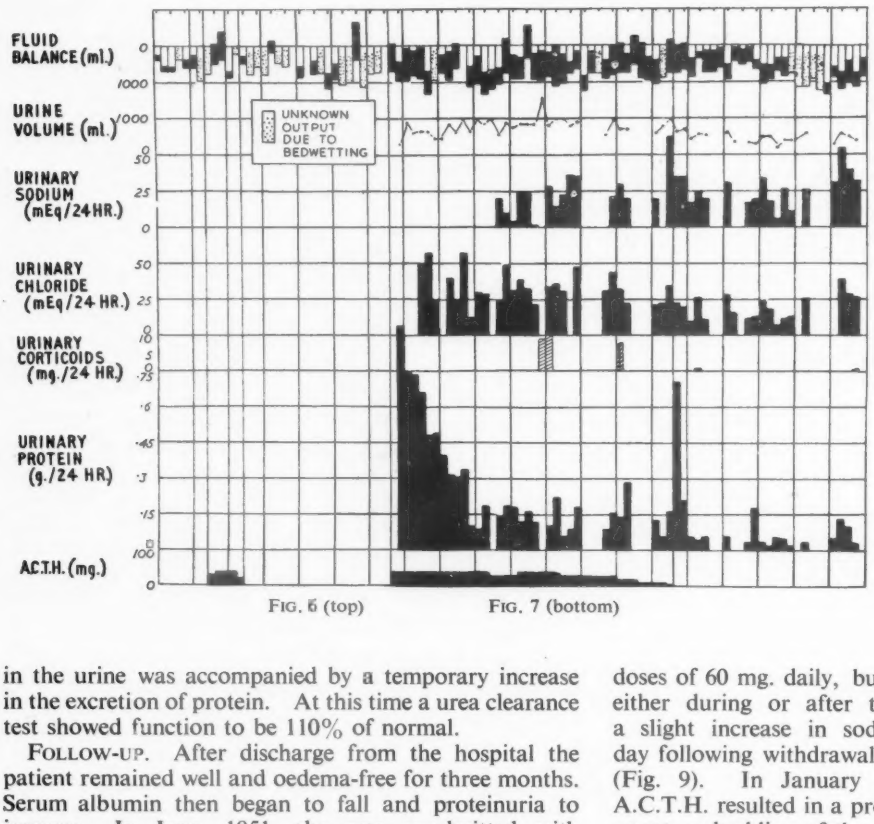

FIG. 7 (bottom)

in the urine was accompanied by a temporary increase in the excretion of protein. At this time a urea clearance test showed function to be 110% of normal.

FOLLOW-UP. After discharge from the hospital the patient remained well and oedema-free for three months. Serum albumin then began to fall and proteinuria to increase. In June, 1951, she was re-admitted with oedema, with a serum albumin concentration below 1 g. per 100 ml. and an elevated cholesterol level. At this time red cells in small numbers were appearing almost daily in the urine. Diuresis followed a four-day course of A.C.T.H. in doses of 60 mg. daily, but only on the fifth day after cessation of therapy. Oedema and haematuria cleared completely, and serum albumin values rose.

In September a six-day course of A.C.T.H. in dosage of 100 mg. daily was without effect. However, three weeks later diuresis followed an 11-day period of hormone therapy, the onset occurring on the fourth day after A.C.T.H. was discontinued. At the time of writing 20-30 red cells per high power field are present in the urine. There has been no decrease in proteinuria following therapy, and oedema is beginning to recur.

Case 6. D.L., a white boy of 12 years, was first admitted to this hospital on September 5, 1950, with oedema of eight days' duration, albuminuria and an elevated serum cholesterol and a lowered serum albumin concentration. Without treatment other than restriction of salt he had a spontaneous diuresis, and was discharged free of oedema but with persisting, although diminished, proteinuria and with abnormal, though improved, serum biochemical findings. In November, following repeated sore throats, he was re-admitted, very oedematous and with serum biochemical values which had worsened in the interval (Fig. 8). He was given A.C.T.H. for 10 days in doses of 60 mg. daily, but showed no signs of diuresis either during or after therapy. Although there was a slight increase in sodium excretion on the third day following withdrawal, no other changes were seen (Fig. 9). In January a slightly higher dosage of A.C.T.H. resulted in a progressive fall in the eosinophil count, a doubling of the total white count and a rise in urinary corticoid excretion. Urinary sodium and chloride levels, which had shown a sudden unexplained increase for three days before A.C.T.H. administration was begun, continued to be excreted freely while A.C.T.H.

was being given. On the last day of therapy urine volume rose steeply, and immediately after the hormone was withdrawn a profuse diuresis of salt and a marked decrease in protein excretion were observed. All oedema fluid was discharged in three days. The child lost 20 lb. in weight and at the end of diuresis his severe malnutrition was strikingly apparent.

Eosinophils reached their highest post-treatment value on the third day after therapy was discontinued. On this day the excretion of formaldehydogenic steroids was within normal limits for this patient. During the next two months the serum cholesterol concentration and the sedimentation rate showed a gradual and progressive fall. The serum albumin concentration, which had risen to 3 g. per 100 ml. one week following therapy, tended to remain up, though fluctuating a little. Sodium retention did not recur, and on January 26 and 27 added dietary salt was excreted without difficulty. There was at no time any sign of oedema, but the patient ate extremely well and gained 10 lb. in weight. Proteinuria did not show further improvement.

In April, 1951, A.C.T.H. was again administered in an attempt to lessen albumin loss through the kidneys. A two-week course was followed by a considerable diminution in proteinuria. After this the patient was discharged, and for six months has remained free of oedema, with normal serum concentrations of albumin and cholesterol, and a normal sedimentation rate. A mild degree of albuminuria remains.

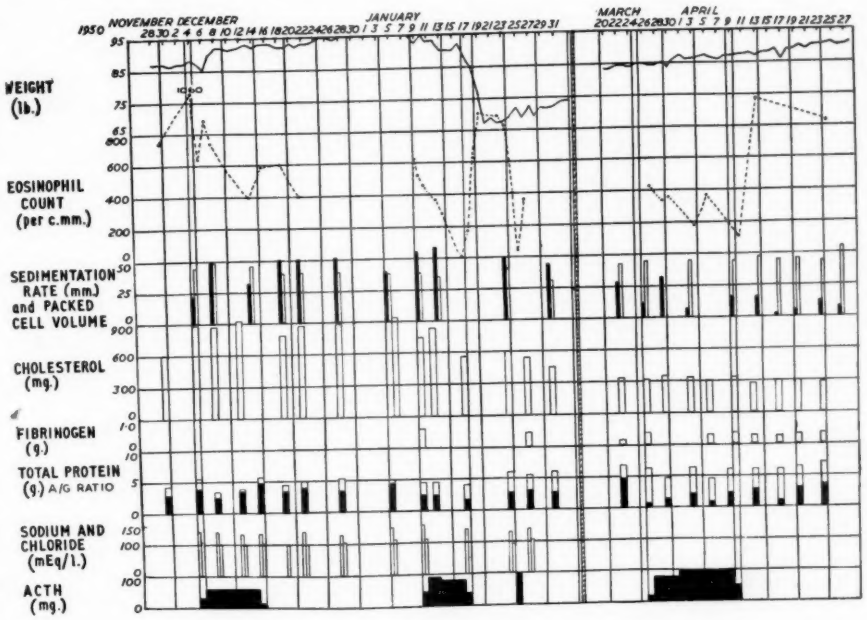

FIG. 8 (top)

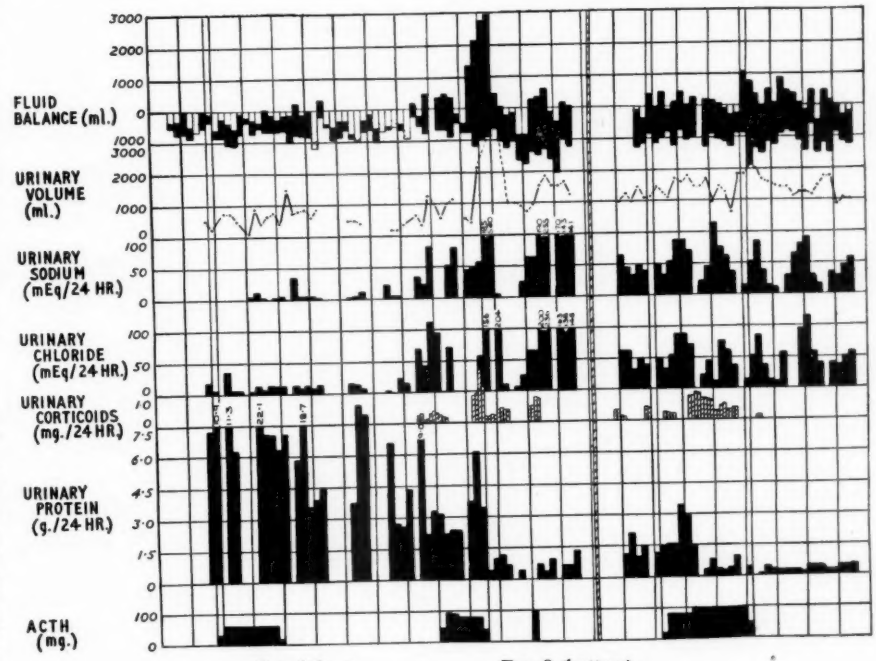

FIG. 9 (bottom)

Case 7. J.S., a 4-year-old white boy, first developed generalized oedema at the age of 18 months. He was admitted to hospital then, and again at 2 years of age, in another city, with the diagnosis of nephrosis. He remained fairly well until February, 1951, when oedema returned for two months. On May 18, immediately after an upper respiratory infection, he was admitted to the Children's Memorial Hospital with puffiness of the face and eyelids and moderate ascites. Investigation showed an albuminuria of 1 g. per 100 ml. with 1-3 red cells per high power field, hypoalbuminaemia, hypercholesterolaemia and an elevated sedimentation rate. Urinary volume was very low, as was the excretion of sodium and chloride (Figs. 10 and 11).

Five days after admission a spontaneous diuresis occurred, which resulted in a loss of 5 lb. weight, partial disappearance of ascites and a fall in serum cholesterol level (Fig. 10). Diuresis lasted four days. On its

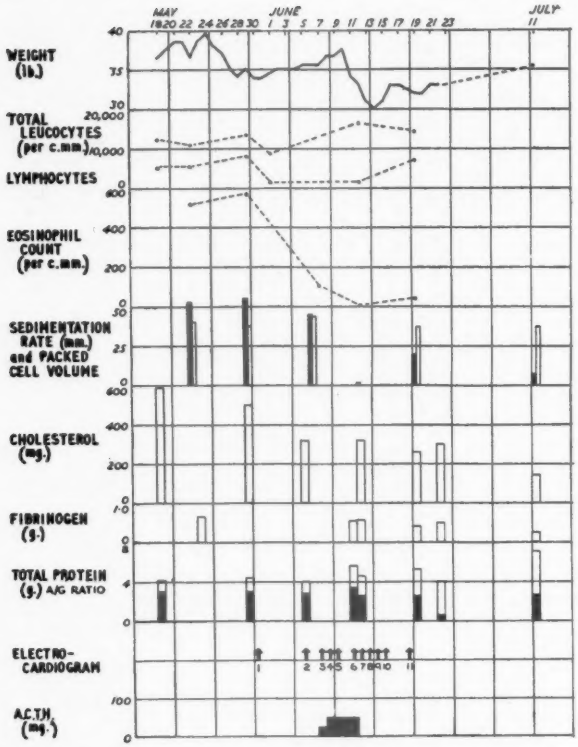

FIG. 10

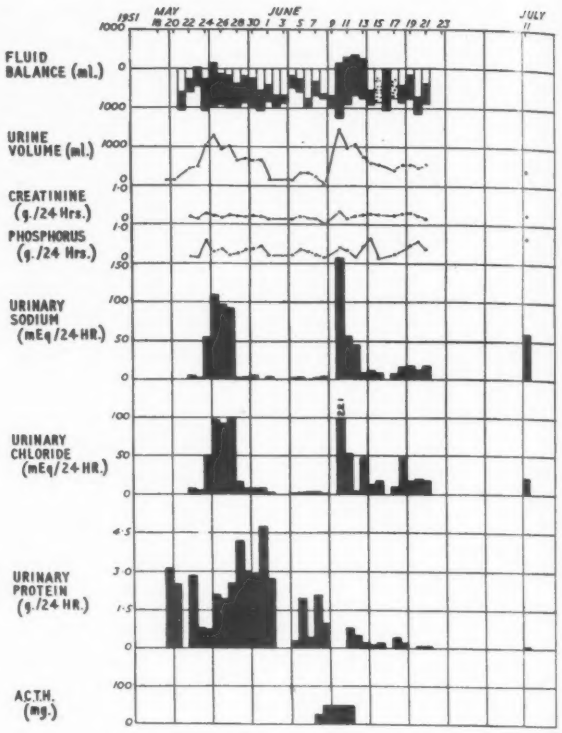

FIG. 11

completion oliguria immediately recurred, as did marked sodium and chloride retention (Fig. 11). A.C.T.H. was given between June 7 and 12. On June 10, after three days' therapy, urinary volume showed a large increase as did the urinary concentration of sodium and chloride, marking the onset of a four-day diuresis. Oedema and ascites had completely cleared two days after therapy was discontinued. A week later serum albumin concentration had returned to normal and proteinuria, though still present, was minimal.

It is noteworthy that on the day A.C.T.H. therapy was started this child seemed weak and listless. Electrocardiograms taken some days before, after his spontaneous diuresis, had shown some depression of T-waves. Repeat readings on June 5 and 7, before any A.C.T.H. had been given, showed almost flat T-waves. There was an immediate response to oral potassium, both clinically and by electrocardiogram. The potassium-excreting effect of A.C.T.H., acting in a period of potassium deficiency following on his spontaneous diuresis, necessitated the giving of relatively large amounts of potassium during therapy in order to prevent the disappearance of T-waves. On June 11 the serum potassium level was only 3 mEq/litre after the child had received 37 mEq of potassium daily since June 8.

FOLLOW-UP. Following discharge from hospital in June, 1951, the patient remained well. Four months after therapy there was no oedema, the urinary protein loss was 0·23 g. and he was excreting sodium normally. The serum cholesterol measured 288 mg. and serum albumin 3 g. per 100 ml. Although the patient had had a number of mild upper respiratory infections he had not re-accumulated oedema.

Results

Spontaneous Diuresis. Three patients partially or completely lost their oedema following infections while under study (Cases 1, 3 and 7). At the onset of a non-bacterial pneumonia the initial rise in temperature of the patient S.S. (Case 1) was accompanied by a fall in eosinophils to zero (Figs. 1 and 2). Eosinophils remained very low for eight days, at which time urine volume and chloride excretion simultaneously increased and diuresis began. Over the following three weeks all oedema was lost. A slight increase in the concentration of serum albumin and some decrease in the serum cholesterol concentration were observed immediately following diuresis.

C.A. (Case 3) also spontaneously discharged oedema fluid on the ninth day after the onset of a febrile illness (Fig. 4), with resultant partial loss of swelling. Again a temporary increase in serum albumin and fall in serum cholesterol concentrations occurred. These latter changes became even more marked following a second rise in fever which also produced a reduction in eosinophils.

The urinary output of J.S. (Case 7) showed a sudden increase a few days after admission to hospital (Fig. 11). At this time the excretions

of sodium and chloride rose steeply and remained elevated for several days. Diuresis was not complete, nor were the biochemical values of the serum improved following this spontaneous loss of fluid. It is of interest in this patient that the washing out of potassium occurring during spontaneous diuresis, in conjunction with a low potassium intake due to anorexia, resulted in marked lowering of the serum potassium concentration, electrocardiographic changes, and marked lassitude and weakness.

D.L. (Case 6) also underwent spontaneous diuresis during his first admission to the hospital two months preceding treatment with A.C.T.H. In none of the above cases has spontaneous diuresis resulted in duration of the oedema-free state for more than a few days. It is possible that longer and more marked stimulation of the adrenal is necessary to produce more than transitory loss of oedema, freedom from sodium retention and elevation of serum albumin. Such a strong stimulus may be the mechanism of the diuretic response seen following measles, septicaemia and other severe infections.

Dosage of Cortisone and A.C.T.H. Optimal dosage being unknown, cortisone was administered to the early cases in low doses. Case 1 received 615 mg. over a nine-day period, and Case 2 the same amount over a 10-day period. There was no significant change in the first child's condition during or after therapy (Fig. 1), but one week following withdrawal the sedimentation rate fell suddenly to normal, and the serum albumin concentration was found to have doubled. M.P. (Fig. 3) developed so much increased oedema and ascites that abdominal paracentesis was performed. The non-protein nitrogen rose to 45 mg. per 100 ml., serum albumin increased and serum globulin decreased slightly on the day following withdrawal. It was extremely difficult to collect this patient's urine, but it is doubtful if any true diuresis occurred.

A somewhat larger dose was used in Case 4, 800 mg. being given over an eight-day period (Fig. 5). Paracentesis had become necessary on the day before therapy began, hence there was no weight gain during cortisone administration. Actual diuresis occurred between the second and fifth days of therapy, possibly as a result of pneumonia contracted 12 days previously. Immediately following withdrawal of the hormone there was an increased urinary output for three days, but no true diuresis. A fall in sedimentation rate and a temporary rise in serum albumin, as well as a slight rise in serum cholesterol concentration occurred.

There having been no diuresis in Cases 1 and 4 as a result of their first courses of cortisone, larger doses were given during the second period of therapy (Figs. 2 and 5). C.A. (Case 3) also received the larger dose during his initial course (Fig. 4). More marked fluid retention occurred during therapy but the ensuing diureses were complete, and weight loss was marked.

A.C.T.H. (Armour) in doses of 40 mg. daily resulted in complete diureses in two children, aged 3 and 4 years respectively (Figs. 7 and 10). A daily dose of 60 mg. given for 10 days was ineffective in a 12-year-old boy, whereas 80 mg. resulted in diuresis (Fig. 9). Later, when this same patient was oedema-free the administration of 80 mg. daily had no effect on proteinuria, whereas 100 mg. daily reduced the daily excretion of protein from 1·5 g. to 200 mg. or less (Fig. 9).

Diuresis. Oedema was not dispersed following three courses of cortisone (Figs. 1, 3 and 5) and one course of A.C.T.H. (Fig. 8) in all of which the dose used was a trial one, and insufficient. Diuresis began between the second and eighth days after withdrawal of cortisone, and as early as the third and fourth days of A.C.T.H. therapy.

Leucocytes. In all cases a substantial rise in the total leucocyte count occurred during cortisone therapy, increases of 7,000 or 8,000 cells per c.mm. being common. The lymphocytes showed a preliminary slight decrease, then either rose somewhat or remained unchanged. The above changes reverted to normal about two weeks after therapy was discontinued. Although not charted, increases in the total leucocyte count occurred similarly in patients receiving A.C.T.H. The A.C.T.H. dosage, which was insufficient to lower the eosinophil count adequately and to produce clinical effects, was also ineffective in raising the total white count. In Case 5, which received A.C.T.H. for six weeks, the total leucocyte count remained consistently at 16,000 until the patient developed an intercurrent infection. With the rise in fever to 100° F. there was an increase in the white count to 40,000. A concomitant rise in the eosinophil count to 750 per c.mm. remains unexplained, but may represent a temporary state of relative adrenal hormone lack due to increased demand for hormone during infection. Antibiotic therapy resulted in a rapid fall in fever to normal, and a reduction in the white count to 20,000 and the eosinophils to less than 30 per c.mm.

The infections which resulted in fever, eosinpenia and diuresis in Cases 1 and 3 were not accompanied by any marked rise in the total white count, and were presumably of virus origin. In viral infections, although the adrenal is apparently stimulated, some factor prevents the leucocyte rise which otherwise occurs when circulating eosinophils are markedly depressed.

Eosinophils. In response simply to fever and infection there occurred an immediate drop in the eosinophil count to levels just above zero. Eosinophils were maintained at low levels for as long as one week following the onset of pneumonia in Cases 1 and 3 (Figs. 1 and 4), and during the various intercurrent infections developing in Case 2 (Fig. 3). However, the administration of 300 mg. of cortisone daily for three days did not reduce the eosinophil count below 60 to 70 per c.mm. in two of the children (Figs. 1 and 5). These children had both received a previous course of hormone therapy a short time before. It has been our experience that a second course of hormone may result in less eosinopenia, and may even cause the eosinophils to rise. In a previously untreated child (C.A., Fig. 4), eosinophils virtually disappeared in 48 hours on a dose of 300 mg. daily.

High pre-treatment eosinophil counts, as noted by Luetscher and Deming (1950), were seen in three patients (Cases 5, 6 and 7). Two of these had a history of allergy. In D.L. (Fig. 8) the original very high count was present again within a day or two after A.C.T.H. was discontinued. During diuresis the counts tended to return to previous levels, except in the case of spontaneous diureses where low eosinophil levels were seen throughout the period when oedema fluid was being discharged (Figs. 1 and 4).

Sedimentation Rate. The erythrocyte sedimentation rate was uniformly elevated on admission. In three children (Cases 1, 2 and 3) little consistent change occurred during the hospital stay. C.A. (Case 3) showed improvement after leaving hospital, and nine months after discharge had a normal sedimentation rate. Case 4, on the other hand, showed a gradual progressive diminution in sedimentation rate in response to cortisone (Fig. 5).

The three patients treated with A.C.T.H. have also shown a slow gradual reduction in sedimentation rate. This improvement, in Cases 5 and 6, followed one or more courses of A.C.T.H. given during the non-oedematous stage (Figs. 6 and 8). In both these children a first course of A.C.T.H., which resulted in complete diuresis and was not followed by early relapse, failed to lower the sedimentation rate. In Case 7, on the other hand, after one course of A.C.T.H., the sedimentation rate fell and has remained normal. Case 6 later relapsed with a return to a high rate, together with other abnormal findings. The sedimentation rate fell again when he responded to re-treatment.

In two patients (C.A. and S.F.), who, after cortisone therapy, are apparently in remission, sedimentation rates were normal nine months after treatment.

Serum Proteins. After cortisone the concentration of serum albumin consistently, though temporarily, increased. This change was usually, though not always, accompanied by a decrease in serum globulin concentration. The increase in serum albumin concentration was usually evident shortly after the cessation of therapy, and there was often a further increase following diuresis. In one child (Case 4, Fig. 5) this initial improvement was maintained, both albumin and globulin being within normal limits at two, six and nine month intervals after discharge. In C.A. (Fig. 4) serum albumin rose following therapy, decreased again soon after, and for the next three or four months remained below 2 g. per 100 ml. Six months after therapy it had risen to normal.

All three A.C.T.H.-treated patients showed an increase in serum albumin, two while on therapy and the third after diuresis. Thereafter, although the patients were oedema-free, there was considerable fluctuation in the albumin level. These changes could not be correlated with variations in the haematocrit or in the degree of proteinuria in Case 6. In Case 5 serum albumin rose steadily and remained within normal limits under a prolonged course of A.C.T.H. which reduced proteinuria to a minimum. Improvement was maintained for two months after the end of therapy, when proteinuria increased and the concentration of serum albumin again fell to below 2 g. per 100 ml.

An increase in serum albumin was observed following infection in two children who received no hormone therapy. This increase was noted at the end of the period of diuresis, two weeks after the fall in eosinophils which accompanied the initial spike of fever (Figs. 1 and 4).

Serum Electrolytes. No consistent change was noted in either serum sodium or chloride concentrations during or after therapy.

Serum Cholesterol. No consistent change in serum cholesterol concentration was noted during periods of therapy except in Case 5 where prolonged A.C.T.H. therapy resulted in a progressive fall in cholesterol. In all cases except two, however, (Cases 1 and 2), serum cholesterol fell rapidly or slowly to normal, or almost normal values after diuresis had occurred. Case 2 received inadequate therapy, .and no change occurred in his weight. Case 5 relapsed later, but in Cases 3, 4, 6 and 7, the cholesterol has remained normal.

Urinary Protein. Cortisone administration appeared to result in a gradual decrease in proteinuria in the one cortisone-treated patient in whom protein excretion was quantitatively measured, the total daily loss in the urine decreasing from 5 g. to 2 g. (Fig. 2). During diuresis, excretion increased

to pre-treatment levels (7 g. protein) for two days, and immediately fell to less than 1 g. per day, a lower protein excretion than at any time during the previous three months. Semi-quantitative tests for urinary albumin in Cases 3 and 4 showed a marked decrease after cortisone was withdrawn, and a further gradual decrease over the following months, with eventual disappearance of albumin from the urine. Proteinuria reappeared in the urine of Case 4 10 months after therapy, and his urine has been alternately negative and positive for albumin on several occasions since.

A sharp decline in proteinuria was noted for varying lengths of time following diuresis in the A.C.T.H.-treated patients. When heavy proteinuria reappeared but before oedema recurred, a prolonged course of A.C.T.H. given to one of the patients (Case 5) caused a gradual decrease in, and virtual disappearance of, protein from the urine (Fig. 7). A similar attempt to abolish proteinuria in the second patient (Fig. 9) was abandoned after 10 days because the patient developed abdominal pain. Protein excretion had by then decreased from 1·5 g. to less than 200 mg. per day. In both patients the decrease was temporary, and albuminuria again became heavy after three to four weeks.

Urinary Sodium and Chloride. Sodium and chloride retention of some degree is characteristic of nephrosis in the oedematous stage. Failure to excrete chlorides normally was noted early in the period in hospital of Case 1, when only 3 or 4 mEq a day were appearing in the urine (Fig. 2). In this case, during both the diuresis which followed infection and that which occurred after cortisone, there was a great increase in the output of chloride, and marked retention did not recur during the period in hospital.

During the oedematous stage in Case 6 the excretion of sodium and chloride was greatly reduced. Three days before the second course of A.C.T.H. was begun the excretion of these electrolytes suddenly increased. Urine volume also rose, remaining high throughout A.C.T.H. administration. On hormone withdrawal a large diuresis of salt and water occurred. Whether this diuresis was A.C.T.H.-induced or was partially due to a spontaneous fluid loss which merely coincided with a period of hormone therapy, is not clear (Fig. 9).

Urinary Corticoids. The excretion of formaldehydogenic corticosteroids was measured in Case 6 before, during and after two short courses of A.C.T.H. The patient had previously been given a course of A.C.T.H. to which he had not responded. Control excretions were within the range expected for a child of his age. On a dose of 80 mg., daily excretion of corticoids rose to five or six times control values. The day following withdrawal of therapy excretions were lower than control values, but rose in the three succeeding days to normal (Fig. 9).

Later, the patient did not respond with an increase in corticoid output to a dose of 80 mg. of A.C.T.H. administered for five days. When the dose was increased to 100 mg., excretion values doubled for three days. Thereafter, with no change in the A.C.T.H. dosage, the amount of corticoids excreted fell to control values. Two days after therapy was discontinued corticoid excretions again were below control values. The excretions of corticoids in this patient did not behave similarly to those reported by Farnsworth (Farnsworth and Dupee, 1951) in patients with nephrosis receiving A.C.T.H. therapy. During the second course of A.C.T.H. the excretions of D.L. (Case 6) were lower than they had been during the first course, even though the dose of A.C.T.H. was somewhat higher during the second course. Farnsworth reports increasing corticoid output during second and third courses of A.C.T.H.

The excretion of these steroids was also measured in Case 5 on several occasions. When the patient was receiving 40 mg. of A.C.T.H. daily the amount of corticoids excreted was about ten times the amount excreted in the month following therapy.

Discussion

There is little knowledge as yet concerning the mode of action of cortisone and A.C.T.H. in the nephrotic state. It is recognized by many observers (Farnsworth, 1950; Thorn, Forsham, Frawley, Hill, Roche, Staehelin and Wilson, 1950; Riley, 1951; Barnett, McNamara, McCrory, Forman, Rapoport, Michie and Barbero, 1950) that A.C.T.H. is capable of producing diuresis in the oedematous patient, either during therapy or following withdrawal. The experience of some investigators (Luetscher and Deming, 1950), as well as that of the present authors, is that similar effects follow the cessation of cortisone therapy. Whether these hormones can influence the nephrotic state apart from precipitating diuresis, by permanently decreasing proteinuria, for example, is not established.

Current concepts of the cause of nephrotic oedema postulate an effort on the part of the kidney to support plasma volume by conserving salt, this saving being an attempt to compensate for the loss of fluid and electrolyte to the tissues which occurs because of lowered plasma osmotic pressure (Bradley, Bradley, Tyson, Curry and Blake, 1950). The conservation of salt is believed to be brought about by increased tubular reabsorption of sodium and chloride, and secondarily of water. In 1948 Farnsworth observed decreased

excretion of both sodium and chloride in nephrotics. Recently evidence has been presented which suggests that the ability of nephrotic urines to cause sodium retention in adrenalectomized animals may be greater than normal (Luetscher and Deming, 1950). The possibility that in nephrosis there may be an increased production of salt-retaining adrenal hormone is also supported by results of recent tissue analyses. Fox and Slobody (1951) demonstrated that muscle of children who had died of nephrosis contained increased amounts of water, sodium and chloride, but were markedly depleted of potassium. These findings are compatible with over-activity of adrenal cortical hormones with salt- and water-retaining effects.

If the mechanisms causing oedema include lowering of plasma osmotic pressure through loss of the albumin fraction of the plasma, and in addition urinary retention of sodium (and of water) to replace electrolyte lost to the serum by passage to the tissue spaces, it would appear that loss of oedema might be brought about by factors opposing the retention of salt, by those favouring its excretion, or by any agent capable of raising the concentration of serum albumin. It is recognized that during the state of adrenal insufficiency sodium is not retained for the body by the kidney. Hence it has been argued that the giving of a synthetic adrenal hormone such as cortisone, which inhibits the release of pituitary A.C.T.H., would, after withdrawal, be expected to result in a state of temporary adrenal insufficiency. That this is at least partially the explanation of the diuresis which follows cortisone withdrawal seems probable (Thorn, Merrill, Smith, Roche and Frawley, 1950; Luetscher and Deming, 1950).

Thorn *et al.* (1950) have pointed out that although the diuresis which follows withdrawal of A.C.T.H. can be similarly explained, another cause must be sought for the diuresis occurring during A.C.T.H. therapy. It is known that not all adrenal hormones are salt-retaining in their effect, and there is evidence that those of the glucocorticoid type may actually be salt-excreting in action. Hence A.C.T.H., which causes the release of glucocorticoids, may release hormones which compete with the salt-retaining type at the kidney tubule. Thorn and his colleagues have also postulated that a kidney tubule, stimulated for some time by A.C.T.H., may eventually become fatigued and no longer able to retain sodium as before. To support this suggestion he cites the decreased sodium retention under deoxycorticosterone acetate (D.O.C.A.) and the failure to respond to pitressin during diuresis, on the part of A.C.T.H.-treated patients.

In the maintenance of plasma osmotic pressure in the nephrotic the amount of albuminuria may be an important factor. Addis, Marmorston, Goodman, Sellers and Smith (1950) showed that experimental proteinuria in the rat could be removed by adrenalectomy, but was aggravated by D.O.C.A. and cortisone. Luetscher and Deming (1950) have shown that nephrotics excrete increased amounts of protein while cortisone is being given, and attribute the decreased proteinuria following withdrawal to relative adrenal insufficiency. Keith, Power, Daugherty and Keith (1950) found an initial increase followed by a decrease in proteinuria while cortisone was being given. Thorn *et al* (1950a) reported that A.C.T.H. increased proteinuria, but later stated that protein excretion decreased under this hormone (Thorn *et al.* (1950b). Lauson, Forman, McNamara, Mattar and Barnett (1951) have recently demonstrated decreased permeability of renal glomeruli to protein after treatment with A.C.T.H. In the present report the marked decrease in proteinuria in two patients receiving prolonged courses of A.C.T.H. has been shown.

Another factor which may be concerned in the response of the nephrotic individual to A.C.T.H. and cortisone is the effect which these hormones exert on the serum protein fractions. Hench, Kendall, Slocumb and Polley (1949) first noted that inverted albumin globulin fractions tended to return to normal under cortisone. This was confirmed by Sprague, Power, Mason, Albert, Mathieson, Hench, Kendall, Slocumb and Polley (1950). Thorn (1949) states that D.O.C.A.-like substances tend to cause an increase in the globulin, and a decrease in the albumin fraction of the serum, whereas glucocorticoids produce the reverse effect. The albumin-raising effect of cortisone in nephrosis was noted by Luetscher and Deming (1950) and has been observed by the present authors both in cortisone-treated and in A.C.T.H.-treated patients. The increase in serum albumin concentration begins during hormone administration before diuresis is initiated.

Summary

Seven children with the nephrotic syndrome were treated, four with cortisone and three with A.C.T.H. Cortisone in doses of 50 or 100 mg. daily intramuscularly did not result in diuresis, but when 300 mg. was given for three days, followed by 100 mg. for seven days, diuresis regularly ensued. The onset of diuresis occurred from two to seven days after withdrawal of cortisone. Diuresis also followed the administration of A.C.T.H. in doses of 40 mg. and 80 mg. daily, and began while therapy was being given.

In most instances diuresis was followed by an increase in serum albumin, lowering of serum

cholesterol, a decrease in proteinuria and a fall in sedimentation rate. In the majority of patients there was a tendency, slight or moderate, to revert to their biochemically abnormal state.

Two patients treated with A.C.T.H. during the oedema-free stage showed marked reduction in proteinuria.

Of the four cortisone-treated patients, one died of an intercurrent infection and another in renal failure. Two are in remission, one completely and the other with albuminuria only.

Of the three A.C.T.H.-treated patients, one shows a persistent tendency to re-accumulate oedema, and has now had five courses of therapy. The other two are apparently well except for moderate proteinuria.

In this small series those patients with the shortest history appeared to respond with a more prolonged and complete remission than patients in whom the disease had been present for longer periods.

An incidental finding of interest was a low serum potassium concentration following spontaneous diuresis. Absent T-waves in the electrocardiograms and marked lassitude accompanied the hypopotassaemia.

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CORTISONE TREATMENT OF NEPHROSIS

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The accepted picture of the nephrotic syndrome is that of a grossly oedematous patient with massive albuminuria but having no hypertension or azotaemia. The amount of albumin circulating in the plasma is greatly reduced, resulting in a fall in the total protein content and a reversal of the albumin/globulin ratio. The cholesterol content of the blood is markedly raised. Little is known of the aetiology of nephrosis itself, or of the spontaneous alterations which may occur in its manifestations. The oedema and albuminuria, for example, may vary dramatically and unpredictably, and occasionally vanish completely to result in the cure of the patient. As regards the oedema, it is suggested that this is caused by a retention of sodium which may in turn be produced by overactivity of the salt-retaining hormones of the adrenal glands. That such a mechanism will produce oedema is known, and is exemplified by the oedema occurring when an excess of desoxycorticosterone acetate (D.O.C.A.) is administered to normal subjects or even to patients with Addison's disease where dehydration and an excessive sodium output characterize the untreated case. Levitt and Bader (1951) have shown that in the extracellular fluids both cortisone (17-hydroxy-11-dehydrocorticosterone) and A.C.T.H. (adrenocorticotrophic hormone) have a sodium-retaining action most pronounced in the first few days of therapy. Furthermore, experimental albuminuria in animals is increased by either cortisone or A.C.T.H. and diminished by adrenalectomy (Addis, Marmorston, Goodman, Sellers and Smith, 1950). It may therefore be accepted that an excess of adrenal hormones contribute to oedema and albuminuria. It has been firmly established that, following an intensive course of either cortisone or A.C.T.H., there is a transient depression of endogenous cortisone production by the patient (Luetscher and Deming, 1950; Kendall, 1951; McIntosh and Holmes, 1951). Presuming that a similar response occurred in nephrotic patients following sudden withdrawal of cortisone or A.C.T.H. it seemed possible that a diuresis from loss of sodium and a lessening of the albuminuria might result. In order to test this hypothesis cortisone was administered to nephrotic patients and observations made on the effects of its sudden withdrawal. Cortisone was preferred to A.C.T.H. because contamination of the latter with antidiuretic hormone of the posterior pituitary frequently occurs and would make alterations arising in the water balance of the patients difficult to interpret.

Method of the Present Investigation

Six cases of nephrosis admitted to the Royal Hospital for Sick Children, Glasgow, were chosen for study. All conformed to the following criteria: (1) persistent oedema with ascites; (2) albuminuria exceeding 12 g. per litre; (3) reduction in serum protein content with reversal of albumin/globulin ratio; (4) a cholesterol content of more than 250 mg. per 100 ml. of plasma; (5) the body weight to be stationary or rising for 10 days before starting treatment; (6) the non-protein nitrogen content of the blood to be less than 40 mg. per 100 ml.; (7) the systolic blood pressure to be less than 115 mm. of mercury.

All six cases were treated with large doses of cortisone, the hormone being stopped abruptly to induce the maximal rebound effect. At the time of writing all the cases have been under observation for at least eight months after treatment. Two of the cases received second courses of the hormone, distinguished in the text and tables by an asterisk. One case responded by diuresis on both occasions (J.H. and J.H.*), the other responded on neither (F.M. and F.M.*). The following observations are therefore based on eight courses of cortisone given to six patients with nephrosis. The patients, whose ages varied from 17 months to 7 years, were confined to bed and received a diet which contained less than 0·5 g. (22 m Eq.) of sodium per day for at least one week before and for several weeks after the period of study. The cortisone was given intramuscularly for a five-day period in doses varying from 100 to 300 mg. per day according to the expected weight of the patient, along with 2 g.

of potassium chloride daily by mouth. This dosage of cortisone resulted in a marked depression of the circulating eosinophils during seven of the eight courses, the exception being J.H.*. The patients were weighed each day and the urinary output of albumin measured by the Esbach method. In such young patients the collection of the total urinary output over the prolonged period of the investigation was considered impracticable and was not attempted. Samples of blood were withdrawn before, during and after the cortisone therapy. The total serum proteins were estimated on these occasions and fractionated by the electrophoretic technique suggested by Cremer and Tiselius (1950). The non-protein nitrogen and plasma cholesterol were also estimated. In four cases measurements of plasma volume and blood volume were made by the Evans blue (T1824) method for hyperlipaemic sera described by Chinard and Eder (1948).

The Results of the Investigation

The effects of cortisone on oedema, albuminuria, serum proteins and cholesterol are discussed under separate headings. The details of the case histories are given in the summaries appended.

Effects of Cortisone on Oedema. Alterations occurring in oedema are best judged by changes in the body weight. During the period of cortisone treatment there was some increase in the oedema on five of the eight occasions; in no case was the increase striking, the greatest gains in weight being in J.H. and F.M. whose weight increased by 1·1 kg. each. It may be significant that in three of the four cases where the subsequent diuresis was most marked the weight during cortisone therapy either fell or remained unchanged.

On five occasions diuresis occurred within 12 days of stopping the cortisone; in some cases the diuresis was extreme, in J.N. amounting to 9·2 kg. or 32·3% of his original weight. In three instances where diuresis did not occur the weight continued to rise even after the cortisone was discontinued. Detailed information will be found in Table 1 where a five-day period 14 to 18 days after cortisone was chosen as that period at which the weights of the subjects were constantly lowest. In J.N., J.H. and J.H.* the oedema returned after 67, 17 and 78 days respectively: in R.P. and A.P. it has not recurred after nine months.

Effects of Cortisone on Albuminuria. In all cases the albuminuria increased during cortisone therapy and fell below the original level after the hormone was stopped. That this reduction was due to decreased daily loss of protein and not to dilution of the urine caused by water diuresis can be accepted, since the Esbach reading fell from over 16 parts to less than ½ part in several cases, a decrease out of all proportion to the increase in urinary output. On four of the five occasions when a satisfactory diuresis occurred, marked reduction in the albuminuria was noted within 36 hours of stopping cortisone, and in the fifth case this fall occurred after 72 hours. The maximal diminution in urinary albumin concentration occurred on the fourth, fifth, eighth, ninth and eleventh days after cortisone respectively. In two cases (R.P. and A.P.) the albuminuria disappeared completely and has not reappeared after nine months. On the other three occasions the albuminuria recurred after 14, 26 and 56 days respectively.

TABLE 1

BODY WEIGHT BEFORE, DURING AND AFTER CORTISONE TREATMENT

Case	Mean Weight (kg.) for 5 Days preceding Cortisone Treatment	Mean Weight (kg.) for 5 Days during Cortisone Treatment	Mean Weight (kg.) for 14-18 Days after Cortisone Treatment	Gain or Loss in Weight as % of Original Weight	No. of Days between End of Cortisone and Onset of Diuresis
R.P.	13·8	13·5	11·1	−19·6	2
A.P.	13·2	13·2	10·6	−19·9	5
J.N.	28·5	28·3	19·3	−32·3	5
J.H.	18·2	19·3	13·9	−30·9	6
J.H.*	14·6	15·4	12·3	−15·8	12
C.Y.	23·2	23·5	27·6	+18·9	no diuresis
F.M.	27·5	28·6	29·6	+ 7·6	no diuresis
F.M.*	20·8	21·4	24·8	+19·2	no diuresis

Effects of Cortisone on Serum Proteins. It was intended to measure the total serum proteins before cortisone treatment, at the end of cortisone treatment and on several occasions thereafter but only in four cases was such a complete record obtained. During cortisone treatment the total proteins fell on three occasions and were unchanged in one, but on no occasion was the fall of great extent (Table 2). Four weeks after the end of treatment an appreciable rise had occurred in all

TABLE 2

TOTAL SERUM PROTEINS BEFORE, DURING AND AFTER CORTISONE TREATMENT

Name	Before Cortisone Treatment (g./100 ml.)	At End of Cortisone Treatment (g./100ml.)	Four Weeks after Cortisone Treatment (g./100 ml.)	Three or More Months after Cortisone Treatment (g./100 ml.)	Diuresis	Relapse
R.P.	3·72	—	5·02	5·52	+	0
A.P.	4·14	3·80	5·34	5·92	+	0
J.N.	5·17	—	5·24	4·64	+	+
J.H.	4·29	3·41	—	—	+	+
J.H.*	—	5·12	5·62	4·56	+	+
C.Y.	4·80	4·82	4·29	3·72	0	−
F.M.	4·65	4·56	5·42	5·71	0	−
F.M.*	5·71	3·44	4·84	4·10	0	−

TABLE 3

ALBUMIN AND GLOBULIN CONTENT OF SERUM BEFORE, DURING AND AFTER CORTISONE TREATMENT

Case	Before Cortisone Treatment		Immediately after Cortisone Treatment		Four Weeks after Cortisone Treatment		Three Months after Cortisone Treatment		Diuresis	Relapse
	Albumin (g. per 100 ml.)	Globulins (g. per 100 ml.)	Albumin (g. per 100 ml.)	Globulins (g. per 100 ml.)	Albumin (g. per 100 ml.)	Globulins (g. per 100 ml.)	Albumin (g. per 100 ml.)	Globulins (g. per 100 ml.)		
R.P.	0·58	3·12	—	—	2·27	2·75	3·03	2·44	+	0
A.P.	0·30	3·82	0·22	3·57	2·85	2·49	5·05	0·85	+	0
J.N.	0·31	4·84	—	—	0·48	4·76	0·56	4·08	+	+
J.H.	0·27	4·01	0·21	3·17	—	—	—	—	+	+
J.H.*	—	—	0·37	4·74	2·46	3·13	0·56	3·99	+	+
C.Y.	1·15	3·63	0·48	4·34	0·80	3·50	0·66	3·06	0	—
F.M.	0·95	3·66	—	—	0·50	4·92	0·93	4·75	0	—
F.M.*	0·93	4·75	0·45	2·98	1·17	3·68	0·80	3·31	0	—

cases except one (C.Y.). The greatest rises occurred in R.P. (1·30 g. per 100 ml.) and A.P. (1·20 g. per 100 ml.) and these two are the patients in whom oedema and albuminuria have not recurred. On the other hand, F.M. in whom the total proteins had risen by 0·77 g. per 100 ml., had a higher total protein level four weeks after cortisone than either R.P. or A.P. and yet his oedema was increasing. Three months after treatment R.P. and A.P. showed further increases in total serum protein content; but all the other cases except F.M. had returned to about their pre-treatment levels, with a return of oedema and massive albuminuria.

The various components of the serum protein were measured and these results are shown in Table 3. The α, β and γ fractions of the globulin were estimated separately, but as no significant individual alteration was found the actual detailed figures are not shown.

It will be seen that in every case for which results were obtained the level of serum albumin was lower at the end of the cortisone treatment than before it. Where diuresis occurred, the albumin having first shown a fall, rose to a level far above the original. Indeed from the figures shown in the case of J.H.* one might have expected her to remain as free of oedema as R.P. and A.P. On the three occasions when no diuresis occurred the fall in the level of serum albumin during treatment was succeeded by a much smaller rise which only regained the original level in one case (F.M.*).

In all the patients who were later to have a diuresis, a marked fall occurred in the globulins of the serum some weeks after cortisone treatment: when diuresis did not occur the globulins were little altered. The fractionation shows clearly that the rise which occurred in the total serum protein level in A.P. and R.P. was produced by a very marked increase in albumin content which masked a fall in the globulins. In F.M. the reverse occurred, and the increase in his serum protein content derived from a rise in serum globulin, the serum albumin actually showing a slight fall. Thus the apparent paradox of contradictory clinical results in one of the cases having a marked rise in total serum proteins is explained.

The electrophoretic curves, obtained from these patients' sera, show clearly certain significant changes in the pattern of the proteins. The characteristic alteration in nephrosis is a marked reduction in the albumin and a large increase in the α and β globulins. It should be pointed out, however, that this particular pattern is not specific for nephrosis but may be seen after any form of trauma such as burns, fractures, acute infections or artificially produced nephrosis (Teilum, Engbaek, Harboe and Simonsen, 1951). The effect of cortisone treatment on the serum proteins of three of our cases is shown graphically in Fig. 1. Case R.P. had a diuresis, followed by apparent cure, and her rapid and sustained rise in serum albumin content, coupled with a fall in the serum globulins, is evident. J.N. had a transient diuresis, reflected by a slight rise in albumin, which rapidly regressed to the usual nephrotic pattern. C.Y. had no diuresis and no significant alteration in her electrophoretic pattern following the cortisone therapy.

Having ascertained the quantity of each of the components of the serum proteins contained in a given volume of blood an attempt was then made to determine the total quantity of each protein in circulation. To this end the blood volume was estimated before and after treatment in four patients, two who responded to cortisone therapy and two who failed to respond. From these values and the known content of each protein fraction per unit volume the total quantities in circulation were calculated (Table 4). It will be seen that the marked drop in blood volume which occurred in the cases R.P. and J.N. who responded to cortisone tended to mask the absolute fall in globulin (when measured per unit volume), whilst the actual rise in the absolute level of albumin was, in the same way, exaggerated. Nevertheless, the final level of

TABLE 4

EFFECT ON PLASMA VOLUME AND TOTAL CIRCULATING PROTEIN OF CORTISONE TREATMENT

	R.P.		J.N.		C.Y.			F.M.*		
	Before Cortisone Treatment	After Diuresis	Before Cortisone Treatment	After Diuresis	Before Cortisone Treatment	During Cortisone Treatment	Two Weeks after Cortisone Treatment	Before Cortisone Treatment	During Cortisone Treatment	Two Weeks after Cortisone Treatment
Plasma volume (ml.)	643	591	1,360	1,042	908	979	930	1,069	1,086	875
Total circulating protein (g.)	24·6	30·3	72·9	57·4	44·3	50·8	36·8	62·9	40·1	38·8
Total circulating albumin (g.)	3·8	13·4	4·3	5·0	10·4	4·7	6·1	9·6	5·5	6·9
Total circulating α and β globulin (g.)	17·5	13·3	60·2	40·2	27·3	35·4	24·2	42·8	25·9	25·2
Total circulating γ globulin (g.)	2·6	2·9	5·8	9·4	5·7	7·1	4·4	8·6	4·3	2·7
Total circulating fibrinogen (g.)	0·7	0·7	2·6	2·8	0·9	3·6	2·1	1·9	4·4	4·0

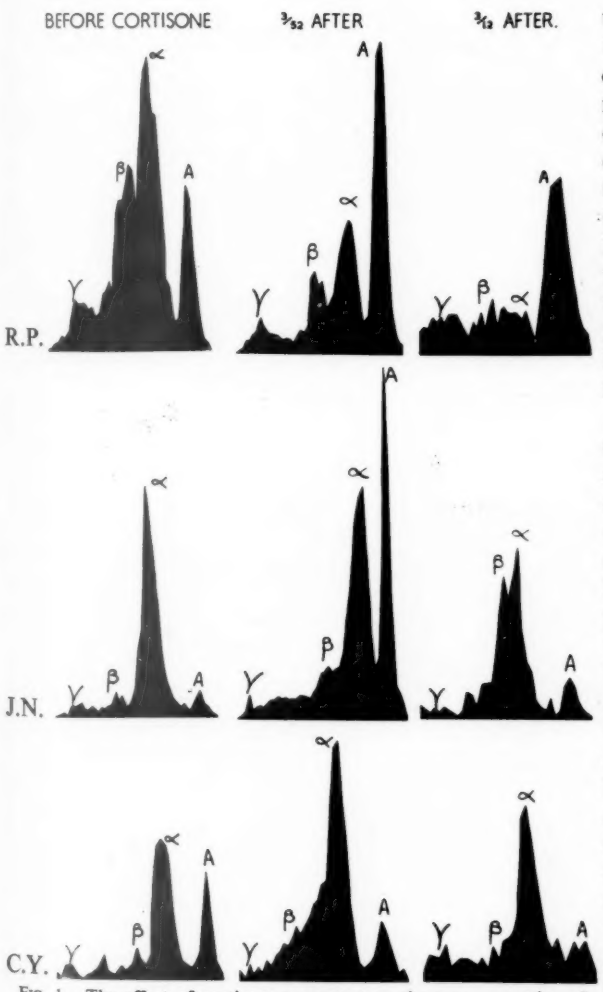

FIG. 1.—The effect of cortisone treatment on the serum proteins of three cases described.

total circulating albumin in R.P. amounted to 13·4 g., the original level being only 3·8 g. This case responded by a diuresis and the disease has not recurred. Unfortunately the blood volume determinations were not completed on A.P., the other case in which oedema did not recur. In the two patients who failed to respond to treatment (C.Y. and F.M.*) there is shown to be a marked fall in the total circulating albumin after treatment, partly masked in F.M.* by the fall in blood volume which took place. Further, it is striking that a marked rise in total circulating fibrinogen occurred in C.Y. and F.M.*, two cases in which diuresis did not occur.

These observations appear to justify a few comments concerning the relationship of the low serum protein level to the albuminuria and the oedema in nephrosis. Several current medical textbooks still suggest that oedema in nephrosis is due to low serum protein levels caused by renal loss of albumin. Such a suggestion appears more plausible when it is considered that the protein loss in the urine consists almost entirely of albumin, that the fall in serum proteins is brought about almost entirely by a fall in albumin, and that albumin has a greater effect on the osmotic pressure of the serum than globulin. That a fall in the level of albumin in the plasma may result from albuminuria is by no means proven; but, in any case, it is improbable that the loss in the urine is sufficient to account for the sustained low concentration in the blood, if production by the liver were continuing at a normal rate. Barnett, Forman and Lauson (1952) have pointed out that the amount of albumin lost in the urine of nephrotic patients is directly proportional to the level of

plasma albumin. It appears to us that the low level of plasma albumin in nephrosis may be in the nature of a protective mechanism intended to minimize the loss of albumin in the urine and, incidentally, lowering the osmotic pressure of the plasma.

These facts are well demonstrated by the case of J.N. after cortisone treatment when, although oedema and albuminuria had both disappeared, the total circulating protein in the blood had actually fallen from 72·9 g. to 57·4 g. and the total circulating albumin had risen by only 0·7 g. (Table 4). At this time the concentration of the total proteins in the serum had risen only from 5·17 to 5·24 g. per 100 ml. (Table 2) and of albumin from 0·31 to 0·48 g. per 100 ml. (Table 3). This evidence that the oedema and albuminuria may disappear without any material alteration in albumin content of the serum is very strong. Furthermore, in J.N. the failure of the serum albumin content to rise despite the cessation of renal loss strongly suggests that some factor is inhibiting the production of albumin.

Plasma Cholesterol in Relation to Treatment. The values obtained for plasma cholesterol levels before, during and after treatment are shown in Table 5. During the giving of cortisone the cholesterol content of the plasma fell on four occasions and remained unchanged in another. A fortnight later the levels showed a tendency to rise slightly: indeed, in one of the two cases in which there was no recurrence of the oedema it showed an appreciable rise from 239 to 444 mg. per 100 ml. only to fall to normal levels three months later. In those patients in whom relapse occurred and in those who did not show a diuresis the level of plasma cholesterol rose to the original high levels within one month after treatment and remained elevated. The two cases with clinical cure (A.P. and R.P.) had normal levels of plasma cholesterol three months after treatment.

TABLE 5

PLASMA CHOLESTEROL IN RELATION TO CORTISONE TREATMENT

Case	Before Cortisone Treatment (mg./100 ml.)	At End of Cortisone Treatment (mg./100 ml.)	Two Weeks after Cortisone Treatment (mg./100 ml.)	Three Months or More after Cortisone Treatment (mg./100 ml.)	Diuresis	Relapse
R.P.	430	—	350	104	+	0
A.P.	620	239	444	132	+	0
J.N.	580	—	528	566	+	+
J.H.	527	446	462	553	+	+
J.H.*	554	484	472	—	+	+
C.Y.	368	320	272	486	0	—
F.M.	496	—	430	—	0	—
F.M.*	303	302	204	295	0	—

Discussion

In the natural course of nephrosis it is well known that spontaneous remission or recovery may occasionally take place. However, the occurrence of diuresis on five of eight occasions after cortisone treatment was stopped is too frequent to be fortuitous. It might be asked whether such diuresis would not have taken place had the hormone treatment been continued. The work of Sprague, Power, Mason, Albert, Mathieson, Hench, Kendall, Slocumb and Polley (1950) on the effects of cortisone treatment on the water, sodium and chloride balance of the human subject strongly suggested that sudden withdrawal is essential, if diuresis is to be produced. Sprague *et al.* showed that depression of endogenous cortisone output existed for several days after cortisone therapy was discontinued. This depression was demonstrated by a diminution of 17-ketosteroid excretion, of the eosinopenic response to injected A.C.T.H. and by the general loss of well-being in the patient. McIntosh and Holmes (1951) confirmed this work and claimed that pituitary A.C.T.H. output was also diminished. These physiological studies were confirmed clinically by Luetscher *et al.* (1951) who found that diuresis occurred after cortisone treatment was stopped in 13 of the 18 cases of nephrosis which they treated with this hormone.

What rôle the 11-oxysteroid group of adrenal hormones plays in the production of nephrosis is difficult to ascertain. It has been shown experimentally that existing albuminuria or nephritis is aggravated and altered by treatment with these hormones. Furthermore, Metcoff, Rance and Nakasone (1951) have shown that hormone treatment of nephrosis (producing adrenal depression) promotes a rejection of sodium by the renal tubular cells. This suggests the possibility that the initial fault may lie in the retention of sodium by these cells, an action potentiated by cortisone and other adrenal hormones. Why excessive action of these hormones should exist, or indeed whether it does exist in nephrotic subjects is not apparent.

Spontaneous remissions often follow acute infections by bacterial or virus diseases. Barness, Moll and Janeway (1950) record that 297 infections occurred in their 161 cases of nephrosis and diuresis followed, one to 15 days after the infection, on 75 occasions. So striking is this sequence of infection followed by diuresis that it has been

suggested that nephrotic patients should be deliberately infected with measles, the most consistent precursor of diuresis, in an endeavour to promote a remission (Blumberg and Cassady, 1947). It would seem that this type of diuresis following infection is so similar to that following the stopping of cortisone therapy that the mechanism must be similar. It is suggested that infection stimulates the endogenous production of 11-oxysteroid hormones *via* the pituitary-adrenal axis, that the diuresis coincides with a sudden drop in circulating hormone and that this relative 'cortisone withdrawal' results in sodium loss and diuresis with diminution of albuminuria.

Our data show that while diuresis followed cortisone therapy in four of six cases of nephrosis treated, relapse occurred in two of these cases in which it would appear that some toxic or metabolic factor has continued to act on the renal tubules and overcome the beneficial results of treatment. The two patients who failed to respond to treatment remain enigmata: that their renal function was not grossly impaired was shown by the normal urea concentration of which their kidneys were capable. The blood proteins and albuminuria appeared to react initially in a fashion similar to the successful cases, but the response must have been incomplete or insufficient in some unrecognized way to overcome the disease process.

The main value of cortisone treatment appears to lie in the ability of the hormone to promote diuresis in a larger proportion of cases than any other treatment (except perhaps A.C.T.H.). Thus cortisone is a valuable therapeutic measure as well as a useful research weapon in the investigation of this fascinating condition.

Summary

Six cases of nephrosis were treated with large doses of cortisone, the treatment being stopped abruptly. In four of the cases a diuresis with loss of oedema and albuminuria followed the termination of therapy. Two of these cases have had no recurrence of oedema or albuminuria and their blood chemistry has remained normal.

It is suggested that the oedema in nephrosis is not primarily due to a diminution in the plasma proteins. Furthermore the low level of blood proteins is not satisfactorily explained by loss of albumin in the urine. It appears probable that there is a reduced synthesis of albumin by nephrotic patients.

Cortisone is considered to be a useful method of provoking diuresis in nephrotic patients.

We are glad of the opportunity to acknowledge our indebtedness to Professor Stanley Graham for his constructive advice and criticism and to both Professor Graham and Dr. J. H. Hutchison for allowing us to study cases in their wards.

CASE REPORTS

Case 1. R.P. was a girl aged 20 months. She was healthy until September, 1950, when generalized oedema and albuminuria developed and she was admitted to hospital. Her weight was then 11·65 kg. and her urine contained 12 g. of albumin per litre and many hyaline and granular casts and a few red blood cells. Her blood chemistry at this time gave a total serum protein content of 4·75 g. per 100 ml. (1·94 g. albumin and 2·63 g. globulin). The plasma cholesterol was 353 mg. per 100 ml. The oedema gradually receded until on December 4 her weight was 9·3 kg., but the heavy albuminuria persisted and pitting was always present in the ankle region despite treatment by a low-sodium diet and various diuretics. She was discharged in April, 1951, still with oedema and albuminuria.

The patient was readmitted in July, 1951, with gross oedema and ascites. Her blood pressure was 110/70 mm. of mercury and her weight 13·7 kg. The urine contained 24 g. of albumin per litre, many hyaline and granular casts, but no red blood cells. As her weight remained high on the low-sodium diet a five-day course of cortisone, 100 mg. daily, was given. Two days after the hormone was stopped her weight dropped rapidly and the albuminuria almost disappeared. By August she was completely free of oedema and albuminuria and weighed 11·86 kg. She was dismissed in September. She has remained free of oedema and albuminuria; she has been seen periodically since, and in May, 1952, was in excellent health with no abnormal findings in her urine or blood chemistry.

Case 2. A.P. was a girl aged 17 months. She was well until aged 16 months when generalized oedema appeared. She was admitted to hospital two weeks later in July, 1951.

She was a well-developed child with marked oedema of the limbs, lumbo-sacral region and face. A moderate degree of ascites was present. No abnormality of any other system was detected. Her haemoglobin was 15·5 g. per 100 ml. blood and her blood pressure 110/70 mm. of mercury. The urine contained 16 g. of protein per litre and many hyaline and granular casts. She was given the low-sodium diet and, as her weight and oedema continued to increase, a five-day course of 100 mg. cortisone intramuscularly was started. Five days after the hormone treatment ceased the albuminuria decreased and a brisk diuresis occurred. Ten days after treatment she was free of oedema and albuminuria and her weight was stabilized at 10·7 kg. She was sent home in August, 1951, and remained very well and free of oedema and albuminuria. In March, 1952, her blood was found to have a normal serum protein and cholesterol content. She was last seen in May, 1952, when albuminuria and oedema were absent.

Case 3. J.N. was a boy, aged 6½ years. His previous health had been good, apart from an attack of bronchitis in January, 1951. In April, 1951, he was noted to have developed oedema and was admitted to hospital.

Examination confirmed the presence of oedema and ascites and of albuminuria amounting to 16 g. per litre. The urine contained a number of hyaline and granular casts but no red blood cells. The blood pressure was 90/50 mm. of mercury. Despite the low-sodium diet the oedema continued to increase and a five-day course of 100 mg. cortisone twice daily was started. Next day a small haematemesis occurred and four days later a low-grade skin infection in the lumbar region appeared and was controlled by penicillin therapy. Five days after cortisone was stopped diuresis occurred and the degree of albuminuria markedly lessened. The albuminuria gradually returned but the boy remained practically free of oedema until July, 1951, when the oedema, ascites and gross albuminuria returned. He was subsequently treated with cation exchange resins and A.C.T.H., both of which produced temporary remissions to be followed once more by oedema and albuminuria.

Case 4. J.H. was a girl, aged 3¼ years. She was healthy at birth and had developed normally. In February, 1951, she developed bronchitis and three weeks later the face, arms and legs became swollen: her urine was noted to be scanty and she was admitted to hospital.

Examination confirmed the presence of marked oedema, ascites and an albuminuria amounting to 18 g. per litre. Some hyaline casts were present in the urine but no red blood cells. Her blood pressure was 100/70 mm. of mercury and no other abnormality was detected on clinical examination. She was put on the low-sodium diet but as the oedema continued to increase, a five-day course of cortisone (225 mg. per day) was given intramuscularly. The albuminuria decreased three days after the hormone treatment ceased and her weight fell markedly. Two weeks later her weight began to rise and oedema and albuminuria became more marked.

A second similar course of cortisone was started in April, 1951. Twelve days after the hormone was stopped diuresis again occurred, the albuminuria having markedly decreased 10 days before. The child remained comparatively free of oedema but the albuminuria later returned and after being sent home she became oedematous again. Later she developed peritonitis and died on July 21, 1951, despite vigorous antibiotic therapy.

Case 5. C.Y. was a girl, aged 7 years. She had grown and developed normally until July, 1951, when she complained of abdominal pain and a sore throat. Four weeks later the eyes became swollen, she became listless and developed anorexia. This gradually receded, then on September 5 the eyes became very swollen and the abdomen enlarged. She was admitted in September, 1951.

She was a well-nourished child with marked oedema of face, limbs and trunk. Ascites was present. Her blood pressure was 110/80 mm. of mercury. Her urine contained 18 g. of protein per litre and granular and hyaline casts but no red blood cells.

She was put on a low-sodium diet, but the oedema and ascites slowly increased and a five-day course of cortisone (100 mg. b.i.d.) was given. Her weight, oedema and ascites became progressively worse both on treatment and afterwards. The proteinuria lessened three days after the cortisone was stopped. A urea concentration test showed a concentration of 3·29 g. per 100 ml. urine on November 9, 1951, proving that renal function still was good. The blood chemistry analysis was repeated in January, 1952, in preparation for treatment with A.C.T.H. but the next day she developed pneumonia which persisted until January 9. Five days later a very marked diuresis with lessening of albuminuria occurred and she lost 6 kg. in weight in eight days. The oedema and ascites completely disappeared and have not recurred but albuminuria was still marked on May 26, 1952.

Case 6. F.M. was a boy aged 5½ years when admitted on July 22, 1951. He had been well until June, 1951, when swelling of the eyelids was noted. Oedema of the limbs and of the sacral region followed and a moderate degree of ascites was detected. No abnormality of the cardiovascular, respiratory or alimentary system was noted. The blood pressure was 115/65 mm. of mercury. The urine contained 18 g. of protein per litre, and many hyaline casts and an occasional red blood cell were present. Despite the low-sodium diet, oedema and ascites increased steadily and a five-day course of 150 mg. cortisone intramuscularly was started. No diuresis occurred but the albuminuria fell to 4 g. per litre for several days after treatment. A second course of 300 mg. cortisone intramuscularly was started in October. Again the albuminuria lessened after treatment but the oedema and ascites continued to increase. The blood pressure was not elevated and urea was concentrated to 2·28 g. urea per 100 ml. of urine.

In November, 1951, 9 litres of chylous fluid were removed by paracentesis abdominis, and the boy's weight, which had been 30 kg. before paracentesis, steadily fell thereafter to 17·8 kg. The oedema and albuminuria still persist eight months later.

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Addendum

Since this paper was written three more cases have been successfully treated, in one of which cortisone was given orally.

RETROLENTAL FIBROPLASIA

BY

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(RECEIVED FOR PUBLICATION MAY 26, 1952)

Retrolental fibroplasia appears to be a new disease. Probably the first cases were recognized in the United States about 1936 but ideas about the disease did not crystallize until Terry first wrote about retrolental fibroplasia in 1942. In his earliest publications he reported infants with bilateral retrolental fibrous masses which appeared during the first six months of life. It was on this finding that Terry proposed the name. He was of the opinion that the condition was the result of a 'fibroplastic overgrowth of persistent vascular sheath behind each crystalline lens'. This pioneer work aroused widespread interest among paediatricians and ophthalmologists. Terry's early death four years later prevented him from joining in the modifications of his original views which are now accepted. He was describing a new hazard of prematurity which, in his experience, resulted in blindness in 20% of infants whose birth weight was below 3 lb.

Owens and Owens (1949) were the first to report on the examination of fundi of premature infants from birth onwards and they observed some of the early changes which eventually progress to the picture of retrolental fibroplasia as described by Terry. Reese and Blodi (1951), also Lelong, Renard, Rossier, Lemasson and Michelin (1951), confirmed the observations of Owens and Owens concerning the early stages of the disease. Reese and Payne (1946), Reese (1949) and Reese and Blodi (1950) in a series of publications made it clear that retrolental fibrous masses occurring in premature infants are rarely the result of either persistent hyperplastic primary vitreous or of retinal dysplasia. The former occurs in full term infants, affects one eye only, is detectable clinically at birth and is not necessarily associated with any other congenital defects. Retinal dysplasia is also found in full term infants but always affects both eyes and is associated with congenital abnormalities in the central nervous and cardiovascular systems.

Material and Methods of Investigation

This report is based upon a study of 56 premature infants suffering from retrolental fibroplasia.

The fully developed pictures of persistent hyperplastic primary vitreous, retinal dysplasia and retrolental fibroplasia are almost indistinguishable, since one retrolental fibrous mass looks much like another. Therefore it is no longer possible to regard the white pupil (leukokoria) as an important diagnostic feature, but it is necessary instead to look for earlier changes in the fundus. In this series the policy adopted in order to detect the earliest retinal changes has been that every premature baby whose general condition allows of it has a thorough ophthalmoscopical examination at the age of 7 days. The pupils are routinely dilated with 1% homatropine and 2½% phenylephrine. Satisfactory examination can be completed without any anaesthetic, but each such examination may take as long as 30 minutes. Giving the infant a teat to suck usually overcomes any resistance to the examination. Only twice has sedation been required (both infants were over 4 months old) and on these occasions rectal pentothal was excellent. Following the first examination each infant is carefully re-examined at weekly intervals until discharged from the premature baby unit. It is not possible to see these babies so frequently once they have left hospital, so as a compromise they are re-examined as outpatients at fortnightly intervals until they reach the age of 6 months. Only by such a regular follow-up can the natural history of this disease be fully unfolded. Examinations at all stages are of course made more often when there is any reason to regard the retina as abnormal. On several occasions the retinal picture has been noted to change beyond recognition in as short a time as four days. The earliest age at which changes were noted was 8 days and the oldest baby showing early lesions was one of 5½ months. It should be pointed out that retinal haemorrhages may, rarely, be present in the eyes of premature

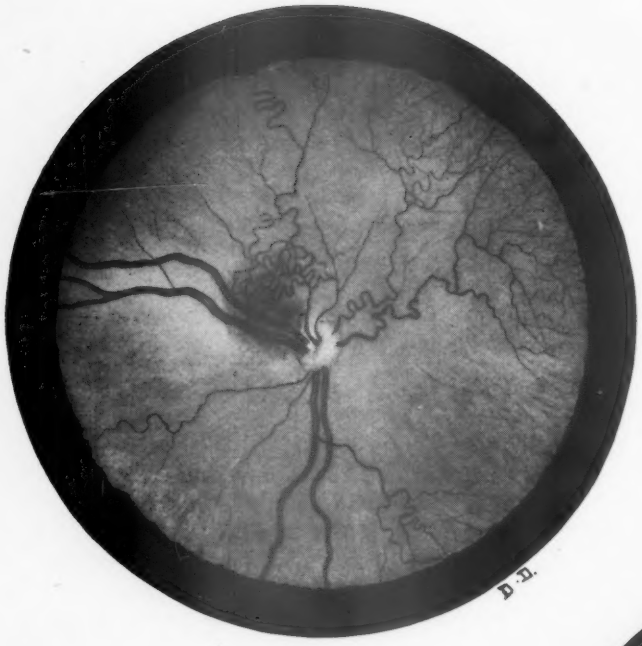

FIG. 1.

FIG. 1.—D.C. Birth weight 2 lb. 11 oz. Age 6 weeks. Right eye. Shows full retinal veins, tortuous vessels, new vessel formation at periphery and a central retinal haemorrhage. This retina was normal 30 days before this drawing was made.

FIG. 2.—E.T. Birth weight 4 lb. 0 oz. Age 8 weeks. Right eye. Shows full veins, slight tortuosity of the vessels, flat retinal detachment in the upper temporal area. There are two folds of detached retina at the periphery and moderate new vessel formation.

FIG. 3.—B.O. Birth weight 3 lb. 8 oz. Age 5½ months. Left eye. Central retinal detachment raised into a fold obscuring the nerve head. This retina was normal two weeks previously.

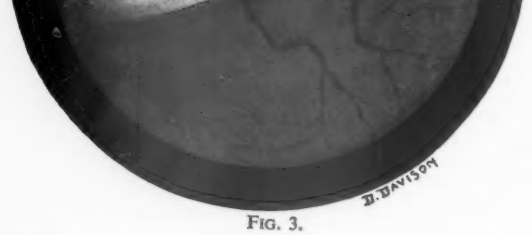

FIG. 3.

infants at the end of the first week, just as they are in some full term infants. These haemorrhages are thought to have occurred during labour; they are absorbed spontaneously without apparent sequelae.

Description of the Disease

As the early stages of retrolental fibroplasia are still relatively unfamiliar in this country it is proposed to outline the development of the disease adding some previously unrecorded features. Figs. 1-6 illustrate many of these. The earliest clinical sign is an excessive fullness of the retinal veins (i.e. exceeding that degree of fullness which is normal for premature infants). Increasing tortuosity of the retinal arteries occurs next, a change which soon involves the veins. The tortuous veins may even

FIG. 2.

form loops (see Fig. 6). The distribution of these changes in the retina is variable; one segment may be involved several days before changes are seen in a neighbouring area. Soon the retina is noted to be oedematous and new blood vessels appear, mainly at the periphery of the retina. All retinal vessels show marked pulsation. Retinal haemorrhages, varying in number, size and distribution, occur in about one quarter of the cases. The vessels mentioned above proliferate rapidly

FIG. 4.—A.J. Birth weight 2 lb. 8 oz. Age 4 months. Left eye. Shows vessel changes as in preceding figures. There are also peripheral haemorrhages and peripheral retinal detachment. In the upper temporal area a vessel is partly obscured by retinal oedema. Three months later this retinal picture was unchanged apart from the absorption of the haemorrhages.

FIG. 5.—E.K. Birth weight 3 lb. 9 oz. Age 3 months. Shows a fine film of new vessels projecting into the vitreous. Note pigment deposits at its edges. Insets show capillary tufts arising from retinal vessels and projecting into the vitreous.

FIG. 6.—E.C. Birth weight 3 lb. 1½ oz. Age 2 weeks. Shows venous ' loop '.

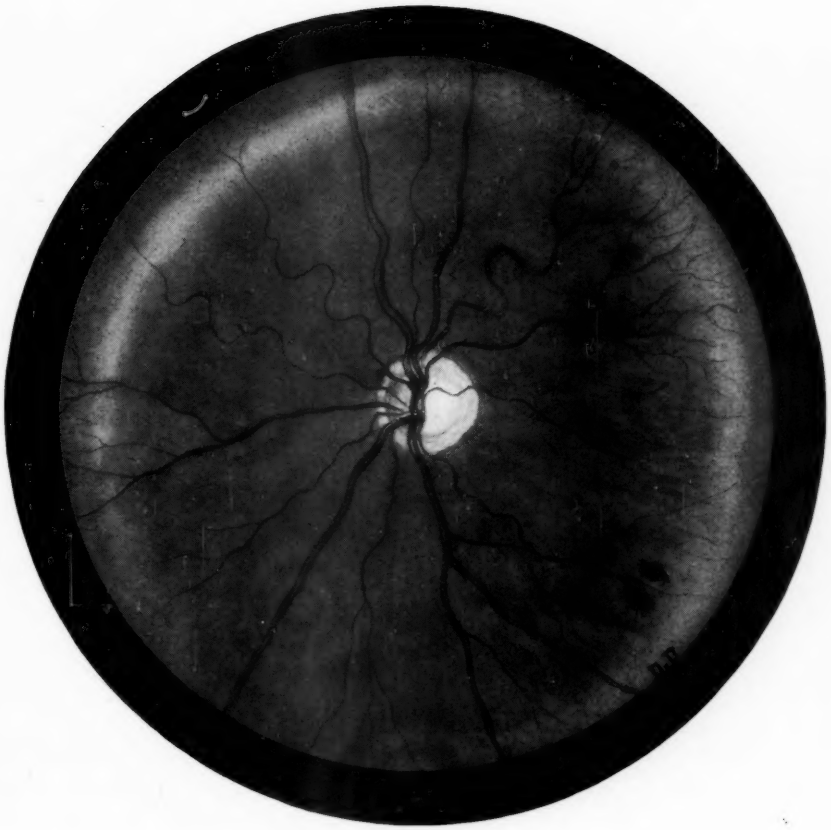

FIG. 4.

and extend into the vitreous as little capillary tufts which are visible ophthalmoscopically. Less frequently these vessels form an extensive, lace-like film (see Fig. 5), also projecting into the vitreous. The edges of such a film may show pigment deposits. A mild and transient papilloedema can usually be observed. By contrast the retinal oedema may become very extensive and as the disease progresses it is associated with detachment of the retina. Commonly, detachments occur first at the periphery and are flat in type but may on occasion be either central or in the form of a fold. If the disease advances fibrous tissue develops at the periphery of the retina. As fibrosis increases it extends across the vitreous obscuring further changes in the retina. The vessels in this new-formed fibrous mass initially appear veiled as if half-buried in a woolly surface: later they become clearly visible along their length. Of 22 babies in whom the disease has been observed from its early stages, i.e. changes in retinal blood vessels only, 70% have not progressed to ' membrane ' formation, the

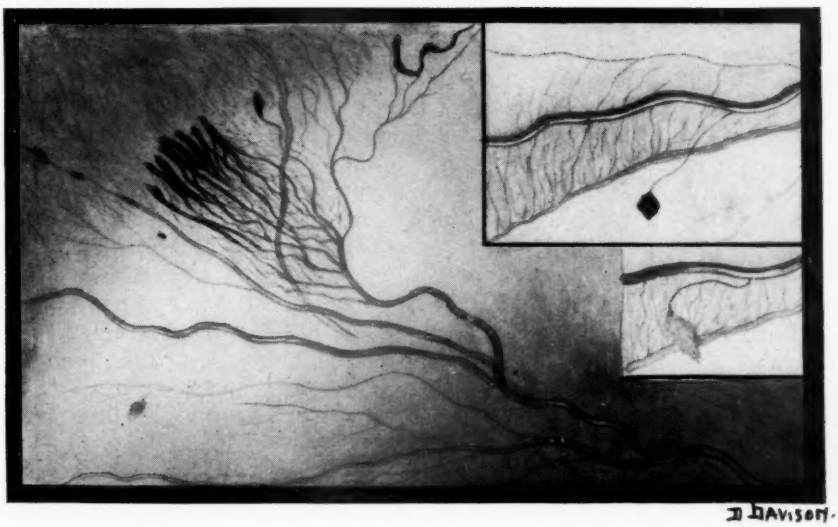

FIG. 5.

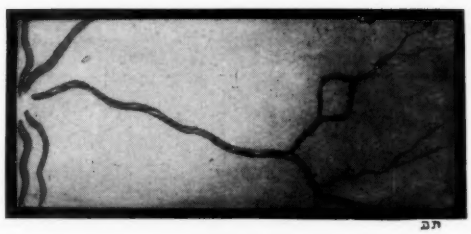

FIG. 6.

disease appearing to have become arrested. Following such an arrest there may be varying degrees of improvement in the retinal picture which may thereafter remain stationary over several months. The time relationships of the various stages are very variable; moreover the phases may overlap. The shortest time in which the eyes have been noted to advance from a normal fundus to a complete leukokoria has been five weeks. To state the longest interval between the first and the final stages would not have an equivalent significance because of the interposed periods of quiescence. The average time from the appearance of early lesions to a leukokoria is about two months.

An attempt has been made to assess the changes in intraocular tension which apparently occur as the disease develops. Initially there is hypotension and enophthalmos; this is a short-lived phase associated with or even preceding the early venous engorgement. The next stage is one of increased intraocular pressure and this stage is associated with the vascular proliferation in the retina. Those cases which go on to ' membrane ' formation concurrently develop a reduced intraocular pressure, enophthalmos and finally microphthalmos. The anterior chamber is shallow from the early stages of the disease.

The late complications of the disease deserve passing mention. The anterior chamber of the eye becomes progressively shallower and may become obliterated, possibly with the development of corneal opacities (though this latter is not a complication which has occurred in this series). In all advanced cases the iris degenerates. The most distressing complication is that of glaucoma; this occurred unilaterally in one infant and necessitated enucleation.

Associated abnormalities do not form part of the picture of retrolental fibroplasia. No increased incidence of cutaneous haemangiomata has been seen, and only one infant had a congenital heart lesion, apparently an interventricular septal defect. Regarding mental development, of 36 babies now over 9 months of age, all but three are apparently mentally normal; these three are grossly retarded.

Incidence

Until 1949 no case of retrolental fibroplasia had been observed among the infants nursed in the premature baby units at St. Mary's and the Duchess of York Hospitals in Manchester. Since then many cases have been discovered and it was therefore decided to review all surviving infants who had been in these two units between January 1, 1947, and December 31, 1951, with a view to discovering the real incidence of the disease over this period. All infants discharged from the units were requested to attend for an examination at the hospital. Of those who failed to do so, some were examined at home. The remainder were not seen, but the fact that the child's vision was apparently normal was accepted when the information came from a health visitor or a reliable mother, provided that the child was over 1 year old. If none of these conditions were fulfilled the case was excluded from the survey.

Satisfactory information was obtained about 629 infants and represents 90% of those still alive when the enquiry was made. Table 1 shows the number of cases of retrolental fibroplasia which occurred in the different weight groups over this period. It will be seen that the incidence has risen sharply. Only one case was found among the older children. The increasing incidence cannot be correlated with an increasing survival rate in these units, for though the survival rate has varied a little over the five years it has developed no definite pattern of change. This finding is in agreement with statements from many centres in the United States (Kinsey and Zacharias, 1949).

In order to learn whether the disturbing incidence of retrolental fibroplasia in Manchester was confined to the premature baby units, those premature infants who were born and nursed outside these two

TABLE 1

INCIDENCE OF RETROLENTAL FIBROPLASIA IN 629 SURVIVING INFANTS SINCE 1947

Year	Under 3 lb.		3–3½ lb.		3½–4 lb.		Over 4 lb.	
	Total Survey	Cases of Retrolental Fibroplasia	Total Survey	Cases of Retrolental Fibroplasia	Total Survey	Cases of Retrolental Fibroplasia	Total Survey	Cases of Retrolental Fibroplasia
1947	4	1	11	0	31	0	72	0
1948	7	0	13	0	27	0	92	0
1949	9	2	18	0	30	0	50	0
1950	16	5	21	2	38	2	75	2
1951	13	12	22	12	30	9	50	9
Total	49	20	85	14	156	11	339	11

units during 1951 were reviewed and examined ophthalmoscopically. No case of retrolental fibroplasia was discovered.

Aetiology

An analysis of the obstetrical notes of the mothers of the affected infants revealed no relevant common factor apart from the onset of spontaneous premature labour. This finding would appear to exclude the possibility that any known disease or treatment of the mother could be concerned in the development of the disease. A similar analysis of the infants' treatment and progress also failed to indicate any common factor other than that all, except one, had been nursed in oxygen tents. Further examination of this factor disclosed that changes in the incidence of retrolental fibroplasia at St. Mary's Hospital had been closely linked with changes in the method of oxygen administration. Before 1949 the premature babies were given oxygen by face mask as a routine and were only in very rare emergencies placed in an oxygen tent. (It is known that the case of retrolental fibroplasia which occurred in 1947 had been nursed in an oxygen tent.) In December, 1949, oxygen tents were introduced on the unit and were used routinely for all infants under 3 lb.; in the following months three cases of retrolental fibroplasia occurred in this weight group. In November, 1950, it was decided to nurse *every* infant on the unit naked in an oxygen tent. Following this, infants whose birth weight was over 3 lb. began to develop the disease. The next change came in March, 1951, when soft plastic covers were introduced for use on the Sorrento-type cot. These made it possible to maintain the infants' temperature without using a tent and resulted in the infants being removed earlier from high tensions of oxygen. Almost synchronous with this change there was a further increase in the number of affected infants of birth weight up to and including 4 lb.; about 75% of the infants in this weight group showed evidence of the disease during this period. It was later discovered that an atmosphere of 80-85% oxygen developed within the tents when the oxygen flow was 2 litres/min.; when the flow was reduced to 0·5 litres/min., which was the minimum rate possible with the apparatus, there was still 60% oxygen inside the tents. Therefore the infants on removal from the tents had been subjected to a sudden reduction in the percentage of the oxygen they were breathing of from 60% to 20%. In October, 1951, the use of oxygen was reduced to a minimum and its withdrawal was carefully graded. Since that time only one serious case and two relatively mild cases of retrolental fibroplasia have occurred. Fig. 7 illustrates these various facts. It should be pointed out that these changes were not deliberately made with a view to influencing the incidence of the disease. The apparent association between variations in oxygen administration and numbers of affected babies has only been discovered in retrospect.

Fig. 8 shows the number of premature infants up to 4 lb. birth weight that survived during each month of 1950 and 1951 in one of Manchester's large maternity hospitals. This hospital contains no specialized units, the premature and full term infants being nursed together. Oxygen tents are not used in this hospital; the infants receive oxygen by face-mask only when necessary. None of these infants has been notified as being blind due to retrolental fibroplasia. In the two premature baby units almost every severe case of the disease progressed to complete blindness and those that did not actually lose all vision possessed definite retinal changes. It therefore seems fair to assume that no severe case of retrolental fibroplasia developed in the infants nursed in this hospital and this assumption is strengthened by the observation that the fundi of about one-third of these infants which have so far been examined are all normal.

Treatment

Treatment of a disease whose aetiology is uncertain has been difficult and largely empirical. In some of our earlier cases we attempted treatment with cortisone and A.C.T.H. Cortisone was given to eight infants of whom seven had a well-developed ' membrane ' at the start of treatment. As might have been expected there was no improvement. The eighth case developed a ' membrane ' during treatment. A.C.T.H. was given to nine infants who had earlier retinal changes. The results in this group were variable. In one infant there was minimal peripheral 'membrane' formation at the beginning of treatment and this progressed to a bilateral leukokoria during treatment. Of the other eight cases, one developed a small area of detachment during treatment and two showed serious extension of the disease after completion of the treatment. In one of these bilateral leukokoria developed and in the other the retinal detachment increased in extent. In the remaining five cases there was an apparent arrest of the disease synchronous with the treatment, and although they are still too young for a full assessment of their vision, apparently see quite well. The potential dangers of cortisone and A.C.T.H. therapy must not be overlooked and must be balanced against the uncertain benefits. In view of the reports by

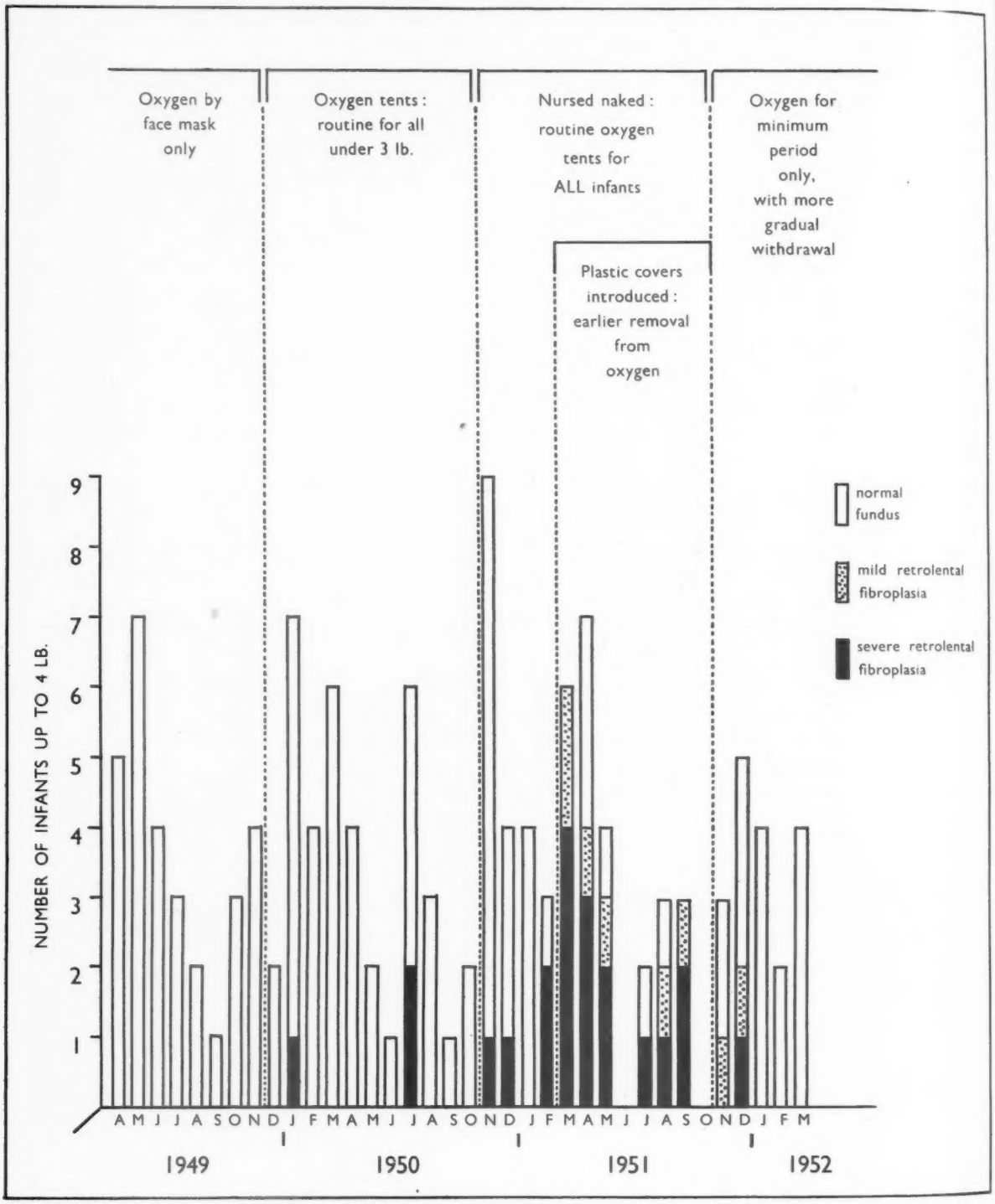
Oxygen by face mask only
Oxygen tents: routine for all under 3 lb.
Nursed naked: routine oxygen tents for ALL infants
Oxygen for minimum period only, with more gradual withdrawal
Plastic covers introduced: earlier removal from oxygen
NUMBER OF INFANTS UP TO 4 LB.
normal fundus
mild retrolental fibroplasia
severe retrolental fibroplasia
A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M
1949
1950
1951
1952

FIG. 7.—Diagram illustrating the incidence of retrolental fibroplasia related to the method of oxygen administration in premature infants at St. Mary's Hospital, Manchester.

Szewczyk (1951) it was decided to treat early cases of retrolental fibroplasia by replacing them in high tensions of oxygen. Six infants have so far been treated in this way with dramatic results. The vascular engorgement disappeared within 48 hours, capillary tufts ceased to be visible and retinal oedema subsided. The speed with which these changes took place greatly exceeded the rate at

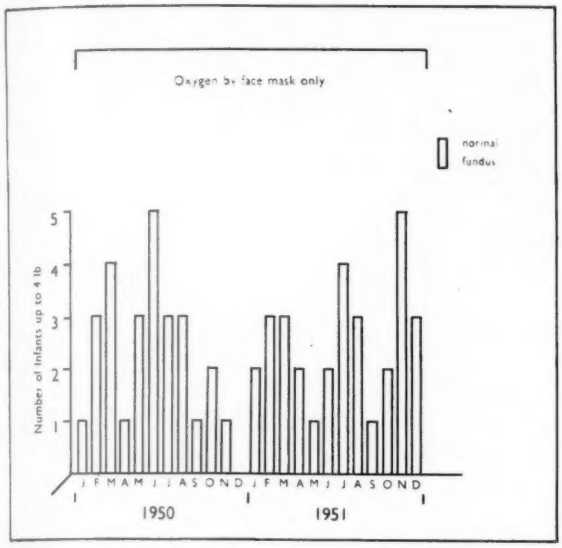

FIG. 8.—Diagram illustrating similar data to that of Fig. 7, but relating to another series of infants treated at a large maternity hospital in Manchester.

which spontaneous regression occurs. Two cases are still in oxygen tents. The other four infants were kept in a high concentration (80%) of oxygen for four weeks and then the oxygen was withdrawn very gradually. In three cases the retina remained normal after the babies were removed from oxygen. The fourth infant's subsequent progress has not been so satisfactory, perhaps because of the more advanced changes with a definite retinal detachment which existed at the time of replacement in oxygen.

Discussion

In the United States a high incidence of retrolental fibroplasia was reported from Boston, and only from Boston, for some considerable time. For example, between 1938 and 1942 in Boston 20% of infants whose birth weight was less than 3 lb. were found to have the disease, whereas in Baltimore between 1935 and 1941 there were no reported cases.

In considering these figures it is necessary to bear in mind the thoroughness with which these infants were followed after leaving hospital; in Boston 85% of the infants were traced as opposed to only 33% in Baltimore (Kinsey and Zacharias, 1949). In addition to the completeness of a survey the criteria of diagnosis are of equal importance in assessing the incidence of the disease. However in the series reported here, if the diagnosis had rested upon a complete leukokoria, thus omitting many cases, an increase in the number of affected infants would still have been obvious (Table 2).

It is of interest that endothelial proliferation is known to occur as a result of anoxia. It remains to be discovered whether such proliferation can be histologically identified in the early phases of this disease. The retinal picture in the early stages presents many of the features suggestive of venous obstruction. Apart from the venous engorgement, the looping of the veins and the capillary tufts are similar to features described by Ballantyne and Michaelson (1947) in obstruction of the retinal

TABLE 2

NUMBER OF CASES PROGRESSING TO LEUKOKORIA

Year	No. of Cases of Retrolental Fibroplasia developing Leukokoria
1947	1
1948	0
1949	2
1950	10
1951	18

veins in adults. The larger lace-like vascular formations projecting into the vitreous seem comparable with those described by Duke-Elder (1940) as occurring with retinal vein obstruction. In studying these cases it has been observed that the longer the venous engorgement lasts the greater is the new vessel formation, and if retrolental fibroplasia has its origin in a vascular obstruction it would seem that the length of time for which this operates determines the final outcome. Presumably only when blood vessels have proliferated into the vitreous can fibroblasts associated with them give rise to the fibrous mass. If on the other hand the obstruction subsides in a relatively short time, the prognosis is good provided that extensive retinal detachment has not already occurred. That such detachment can be disastrous is shown by the fact that one of our cases who has no retrolental membrane is totally blind because of complete retinal detachment.

From this it follows that once we are certain of the aetiology of this process the disease must receive a new name. Even in our ignorance the term ' retinopathy of prematurity ', introduced recently by Heath (1951), has much to recommend it. Without a shift of emphasis to the vessel changes in the retina it is more difficult to include, in an analysis of the incidence of the disease, those cases which have become arrested at an early stage and regress leaving no permanent scar.

The facts summarized by Figs. 7 and 8 suggest that the method of oxygen administration plays an important part in the development of retrolental fibroplasia. In addition the dramatic improvement which has been observed to follow closely upon the

replacement in an oxygen tent of an infant with early retinal changes makes it impossible to ignore the relevance of oxygen tensions in the control of the disease. These two observations might superficially appear to contradict each other. However, they can be reconciled by supposing that retrolental fibroplasia may develop when the tissues of a premature infant undergo a sudden reduction in the tension of oxygen available to them. The initial changes of the disease will, however, rapidly regress when the lowered tension is restored. It would appear that an infant nursed in 60% oxygen and then suddenly transferred to normal air becomes liable to develop the disease, whereas an infant receiving oxygen by face mask only, never having been acclimatized to a high tension of oxygen, cannot subsequently be deprived of it; apparently such an infant does not develop retrolental fibroplasia. (There has been only one exception to this among 56 cases.)

If it is true that the method of administering oxygen is of great importance in the development of retrolental fibroplasia it may be possible to explain the patchy distribution of the cases and the sudden fluctuations in incidence on these grounds. However, this is difficult to do in retrospect, for the exact date of the introduction of apparently minor changes in methods of oxygen administration may be impossible to trace as the details of such changes are often worked out by the sister in charge of the unit and may actually vary with changes in nursing staff.

If the facts put forward here are confirmed by further observations then the problem will no longer involve the search for an aetiological agent and for a satisfactory treatment. Instead it will remain to be shown how it is that a change in oxygen tension, coupled with the physiological processes of the premature infant comes to play such an important rôle in this disease.

Summary

During the past five years 56 cases of retrolental fibroplasia have occurred among premature babies in two units in Manchester. A survey of 629 infants has shown that only three cases occurred before 1950.

The early stages of the disease are outlined. Phases suggestive of venous obstruction are illustrated.

Support is given to the term ' retinopathy of prematurity '.

On six occasions the early changes of the disease have been noted to regress rapidly upon replacing the infant in high tensions of oxygen.

Variations in the method of administration of oxygen appear to be closely linked with the incidence of retrolental fibroplasia.

It is suggested that retrolental fibroplasia can develop when the tension of oxygen available to the tissues of the premature infant is suddenly lowered.

I am grateful to Miss Dorothy Davison for drawing Figs. 1-6. I should like to acknowledge facilities placed at my disposal, also encouragement and advice from Professor Wilfrid Gaisford and from Dr. N. Wells, Dr. S. Guthrie and Dr. A. Holzel; also from Dr. W. Kane and the Manchester Public Health Department.

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A COMPARATIVE STUDY OF THE CIRCULATING EOSINOPHIL LEVEL IN BABIES

Part I : PREMATURE INFANTS

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Studies of circulating eosinophils have been made in many small groups and it has been repeatedly observed that under controlled conditions the circulating eosinophil count may be regarded as a practical clinical test of adreno-cortical function and reserve. The present investigation, the first of a series, was undertaken to find what was the level of circulating eosinophils in premature infants and to study the behaviour of eosinophils in infancy and to find in what circumstances changes in the circulating eosinophil level were effected.

From a preliminary series of daily counts done on premature babies in the Aberdeen Maternity Hospital it quickly became apparent that the circulating eosinophil level in premature infants of the ages of 3 weeks and over was in excess of that quoted as normal for adults by Wintrobe (1946), Whitby and Britton (1950), Forkner (1929) and Washburn (1934 and 1935), but while the final stable level of eosinophils was much higher, this level was only reached after a varying period. In practically all cases counts done on the first or second day of life were extremely low and the rise in eosinophils took place in the ensuing weeks.

To compare this finding with normal infants it was then decided to undertake a series of daily eosinophil counts on full-term infants born in the same hospital. Since these infants were born after the normal gestation period of 40 weeks, the birth weights with few exceptions fell in the 6-8½ lb. weight group and these infants were usually discharged from hospital on the seventh or eighth day. Thus the serial counts for infants in this group are taken over short periods, and the possibility of following these infants for a long period of daily eosinophil counts could not be considered at the time and a prolonged study has not yet been completed. The majority of premature infants had daily counts throughout their stay in the special nursery. The main factor determining the discharge of these infants is the weight, and as a general rule few infants in this nursery are regarded as ready for home before the weight has reached 5½ lb. In this way it has been possible to make long serial counts on 75 infants and watch the steady eosinophil rise in the early weeks of life. It was found that many of these infants before being discharged home reached a stable level of circulating eosinophils, i.e. that daily counts after a time showed little or no fluctuation although each infant had its own individual level.

Technique

The method described by Randolph (1949) for the differentiation and enumeration of eosinophils in a counting chamber with a glycol stain has been used throughout. For each morning's counts equal parts of the phloxine and methylene blue solutions were freshly mixed and allowed to stand for 15 minutes before being used to dilute the blood sample. White cell counting pipettes were used. After thorough cleansing of the skin surface with an ether-soaked swab, peripheral blood was taken from the heel in all infants. The first drop of blood was wiped away and the second drop taken up. The pulp of the heel was not squeezed. No difficulty was experienced at any time in securing an abundant flow of blood from the infants owing to the higher room temperature of both premature and normal nursery accommodation. A simple spring-release lancet was used in preference to a Hagedorn needle.

White cell pipettes were filled to the 0·5 mark with blood and to the mark 11 with diluting fluid, giving a 1 : 20 dilution. For each patient the number of cells seen in four double counting chambers (eight ruled areas giving a total of 7·2 c.mm.) were counted and the average taken. Variations from one ruled area to another occurred but were never exceptionally wide, and there was close approximation between the eight counts in most cases. The counts were made within two hours of the pipette being filled but control counts from the same pipettes left to stand for at least 16 hours overnight gave results practically identical with the first counts. It would seem, therefore, that if counting is

unavoidably delayed fragmentation of cells and clumping of leucocytes with enmeshing of eosinophils is not troublesome with the use of Randolph's fluid. This disadvantage has been reported when Pilot's fluid was used. Immediately before counting the pipettes were shaken for two minutes, then six drops expelled before filling the counting chamber. Three minutes were allowed for the cells to settle. Evaporation is slow when Randolph's fluid is used, and under low power the eosinophil, stained bright red, is easily distinguishable from the remaining white cells which are azure. Eosinophils were counted daily for each infant and as far as possible all blood samples were taken at approximately the same time every day.

The white cell count was made for each infant on the first or second day of life and thereafter at weekly intervals until discharge. The final count made on the day of, or the day before, discharge was the figure on which the percentage of eosinophils was calculated for each child. The same sample of blood was used for the white count as for the eosinophil count and counting chambers with Neubauer ruling used throughout. An average of two ruled areas was taken for each count, i.e. 1·8 c.mm. were counted.

Material

The 75 premature infants, all of whom were born in the Aberdeen Maternity Hospital, conform to the international classification whereby the birth weight of 2,500 g. (5½ lb.) or less is the criterion of prematurity. The group has been subdivided into smaller groups depending on the weight, and the cases fell into these weight groups as follows:

2–3½ lb.	14 infants
3½–4½ lb.	28 infants
4½–5½ lb.	33 infants

Results

Surviving Children. One thousand four hundred and seventy-seven counts were made on 75 infants whose birth weights varied from 2 lb. 2 oz. to 5 lb. 8 oz., an average of 19·7 counts for each child. All infants in the two lower weight groups had a complete absence of eosinophils on the first day but the infants in the 4½-5½ lb. group had an average of 1·3% eosinophils on the first day. The 1·3% eosinophils calculated on the white cell count represents an absolute count of 122 eosinophils per c.mm. From a study of these counts it is evident that the circulating eosinophil level at birth for many premature infants is zero or very close to it, i.e. there is an eosinophilopenia but over the ensuing weeks the eosinophil level rises sharply to reach figures of the order of 1,500 per c.mm. or even higher so that an eosinophilia up to 15% was a common finding (Table 1).

TABLE 1
EOSINOPHIL LEVEL IN 75 PREMATURE INFANTS

Weight Group (lb.)	Number in Group	Average Stay in Hospital (days)	Range of Eosinophils	Percentage of Eosinophils on First Day	Percentage of Eosinophils on Discharge
2½–3½	14	41	0–1,496	0	15·4
3½–4½	28	35	0–1,650	0	15·7
4½–5½	33	17	0–1,496	1·3	11·7

Average white cell count on first day of life: 9,400 per c.mm.
Range of white cell count: 2,800 to 16,500 per c.mm.

On discharge the percentage of eosinophils for the 75 infants was as follows:

1– 4%	12 infants
4·1–10%	48 infants
10·1–12%	8 infants
12·1–16%	7 infants

Thus only 12 infants out of 75 had a percentage of eosinophils within the adult range.

The range over which counts occurred in premature infants was from 0 per c.mm. on the first day of life (and even up to the fifth day in infants whose survival was precarious) up to 1,650 per c.mm. for an infant (of 3 lb. 10½ oz. birth weight) on the forty-fourth day of life. Many of these babies showed a tendency towards the development of a stable circulating eosinophil level during their later counts and close estimations over several consecutive days seemed to indicate that the infant had reached a stable level. Two infants in particular reached their individual levels in the third week of life, and when discharged in the fifth and sixth weeks respectively still had the same levels (Fig. 1). The rise in the circulating eosinophil

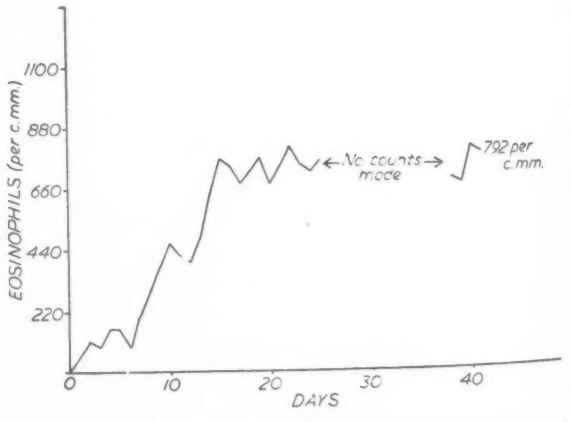

FIG. 1.—Increase in circulating eosinophils to reach a stable level at the fifteenth day. The level was still the same on discharge on the forty-first day. Premature infant (birth weight 4 lb. 8½ oz.).

level was slightly more rapid in the infants in the 4½-5½ lb. weight group but the levels for the other

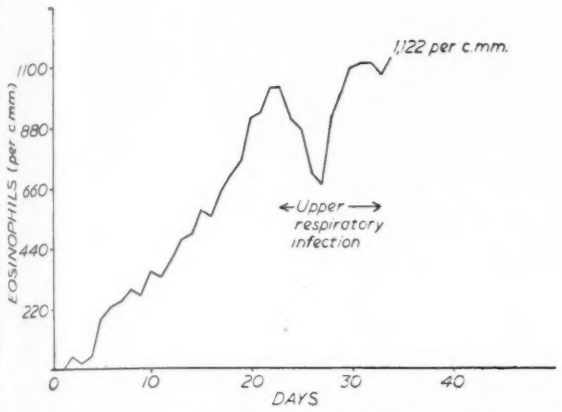

FIG. 2.—Fall in eosinophils during an episode of respiratory infection in a premature infant (birth weight 3 lb. 12 oz.).

two groups were almost identical. Since reproduction of individual graphs for all infants is not practicable, several typical graphs are reproduced and an average curve constructed from available data for each weight group. For the average curves, averages were struck at five-day intervals and the graph plotted from these findings (Fig. 3).

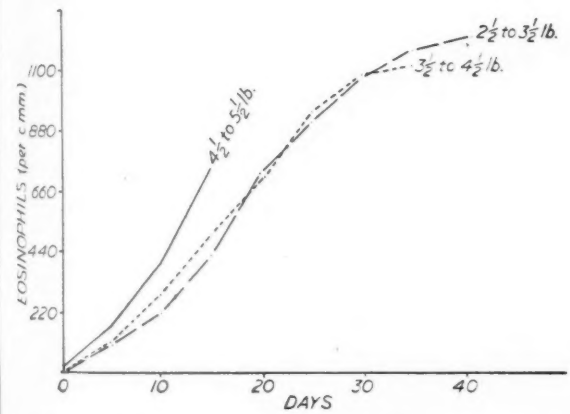

FIG. 3.—Graph of average counts for each of three weight groups.

White cell counts in this study of premature babies numbered 422. Of the 75 infants in the series, 68 had a white cell count made on the first day of life with an average count of 9,400 white cells per c.mm. Twenty-two infants had counts on the twenty-ninth day of life and the average was 11,800 white cells per c.mm.

These figures correspond closely to those quoted by Smith (1951) from Lichtenstein's work where 10 premature babies were examined and 7,500 per c.mm. found to be the average white cell count on the first day of life.

Infants who Died. Twenty-nine counts were made on eight infants who did not survive longer than the thirteenth day. The striking feature in these infants was the persistent eosinophilopenia. In all cases on the day of death there was a complete absence of eosinophils.

Eleven white cell counts were made on these eight infants, but the average count was similar to that of the large group of surviving infants. The white cell count for these infants averaged 8,600 per c.mm. (Table 2).

TABLE 2

EOSINOPHIL LEVEL IN PREMATURE INFANTS WHO DIED

Infant	Age at Death (days)	Daily Eosinophil Counts (per c.mm.)	White Cell Count
T.	3	0, 0, 0.	4,500
W.	3	0, 22, 0.	8,900
T.	4	0, 44, 22, 0.	11,600
M.	5	0, 0, 22, 0, 0.	9,800
H.	4	0, 44, 0, 0.	13,400
Mi.	2	0, 0.	8,900
R.	7	0, 66, 44, 0, 22, 0, 0.	{14,300 12,900
McI.	13	0, 0, 0, 22, 0, 44, 66, 22, 0, 0, 0, 0, 0.	{6,100 4,200

Discussion

The figures for circulating eosinophils in adults vary from author to author. Few recent surveys have been made in children and fewer in infants. Actual figures quoted in the literature for eosinophil counts on infants are rare and only small series have been followed, the best known being the work done by Forkner (1929) on infants but there is no mention made in his work of premature infants. Among the many conditions in which eosinophilia occurs the state of prematurity is mentioned only by Whitby and Newns (1949). Eosinophils may be expressed as the direct count per c.mm. of blood or as a percentage of the total white count. Thus, for adults the direct count is quoted variously as lying between 60 to 200 eosinophils per c.mm. and the percentage accepted as normal is 1 to 4. The higher absolute counts of infants and children are not quoted, but Klein and Hanson (1950) remark that we have come to accept as normal for older children a higher eosinophil level than is quoted for adults. Smith (1951) however says: 'Eosinophils and basophils may occur in the blood smears of earliest infancy in about the proportions represented by these cells in later life'. He does not specifically mention eosinophils in premature infants.

Comparison of percentages of eosinophils shows that the adult figure of 1 to 4 is exceeded unquestionably by the majority of infants in this series. The absolute count for adults is 150 to

400 per c.mm., and Discombe (1946) found that only 1% of normal adults had an eosinophil count exceeding 240 per c.mm. Sixty-three infants in this series had more than 4% circulating eosinophils with direct counts from 376 to 1,650 per c.mm.

The results of serial eosinophil counts were expressed graphically for each patient studied, and consideration of these graphs showed that invariably a premature infant had no eosinophils circulating at birth. This may be closely connected with depression of eosinophils in the mother in the first stage of labour and her eosinophilopenia at delivery (Davis and Hulit, 1949). Where the progress of the infant was entirely satisfactory the eosinophil count rose steadily to reach a high level by the third to the fifth week. Counts were made on eight babies who did not survive (Table 2). It was a constant finding that these infants showed no tendency for the eosinophil count to rise and before death the eosinophil count was 0%. This might be regarded as an indication of an infant's chance of survival, the satisfactory eosinophil rise being indicative of a satisfactory prognosis or, conversely, that the lack of eosinophils could be taken to mean that all was not well with the child.

The eosinophilopenia in infants whose survival was precarious has a parallel in the low circulating eosinophil level of ill children and adults and in the very low post-operative values for eosinophils (Roche, Thorn and Hills, 1950). It has long been accepted that eosinophils appear in increasing numbers with the return of health, and eosinophilia has been described by Lams, quoting Chantemesse and Rey (1899), as ' an index of convalescence '.

In this series of premature infants there were too few instances of infection for the response of the circulating eosinophil level to infections to be studied in detail. One infant, however, with a moderately severe upper respiratory infection in the fourth week of life showed a clear-cut fall in eosinophils. The infectious episode lasted four days, but from the onset of infection seven days elapsed before the eosinophil count was as high as before the first symptoms (Fig. 2). Two other infants with similar infections showed the same pattern of response but less clearly defined, perhaps because the illness was of a very mild character.

Among the infants examined there were seven pairs of twins, of whom two pairs were uniovular. The number of twins studied is too small for any conclusion to be drawn regarding the eosinophil counts but it is of interest that uniovular twins showed serial counts that were almost identical while binovular twins had individual counts showing marked differences. One of the pairs of uniovular twins seen at six months still had similar counts but lower than when the hospital series was concluded.

Summary

Seventy-five premature infants had daily eosinophil counts performed throughout their stay in the Aberdeen Maternity Hospital Special Nursery. Counts were also made on eight premature infants who died.

There is a progressive rise in the eosinophil count from the birth level of zero to a high stable level of circulating eosinophils. This level varied from 900 to 1,650 eosinophils per c.mm. and was reached in three to five weeks.

Infants whose progress was unsatisfactory, and who later died, had a marked eosinophilopenia.

The white cell count of 68 infants on the first day averaged 9,400 per c.mm. and agrees well with figures quoted in the literature. Twenty-nine infants had an average count of 11,200 per c.mm. on the twenty-ninth day.

The percentage of circulating eosinophils in counts done on the day of discharge in this group of premature infants lay between 5 and 12% in 50 of the 75 infants.

It is a pleasure to acknowledge my gratitude to Professor John Craig for his continued help and interest in this work.

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GALACTOSAEMIA

BY

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The terms ' galactosaemia ', ' galactose diabetes ', ' chronic galactaemia ' and ' chronic galactosuria ' have been used more or less synonymously to denote a clinical syndrome characterized by retarded development, hepatomegaly, albuminuria and galactosuria. Cataracts have been observed in some of the cases.

Since the original description by von Reuss in 1908, 14 proven cases of galactosaemia have been placed on record, and 11 other probable but not substantiated examples have been reported. The satisfactory response which may follow treatment before irreparable changes become established makes early and accurate diagnosis a matter of great practical importance. Diagnosis may not be easy on account of the difficulty in identifying the urinary reducing substance, which may be present in only small amounts at any particular time. The purpose of this paper, in addition to recording three further cases, is to demonstrate the diagnostic help given by chromatography.

Case Reports

Case 1. Richard T., aged 12 months, was referred by Dr. George of Haverfordwest for investigation of liver enlargement, defective vision and retarded development. He was admitted to Llandough Hospital in June, 1951.

The only child of young healthy parents, he was born at full term by a normal labour after a normal pregnancy. There was no parental consanguinity and no hereditary or familial disease. The birth weight was 6 lb. 14 oz. During the first month of life he was ill with vomiting and mild but persistent jaundice, and his weight fell to 5 lb. Liver enlargement was noticed at this time. Subsequently he slowly improved, though physical and mental development were tardy. At the age of 2 months a cataract was seen in the right eye. His doctor also found albumin in the urine from time to time, and the presence of some reducing substance was noted.

On admission the baby was under weight (16½ lb.) with bilateral cataracts, the left not so easily seen as the right (Fig. 1). Vision was obviously impaired, but its exact extent was difficult to determine, though a response was obtained to a bright light. Some frontal and parietal bossing was noted, but the anterior fontanelle was normal and no clinical evidence of rickets was found.

FIG. 1.—Case 1, R.T., aged 12 months, showing cataract in right eye.

He was unable to sit up without support, and took little notice of his surroundings. The lower central incisors were erupted. The lower ribs were somewhat splayed, and dilated veins were seen on the upper part of the anterior abdominal wall. The liver was enlarged, hard and smooth; the lower edge reached to the level of the umbilicus in the nipple line. The spleen could not be felt. During his seven weeks' stay in hospital he ran an irregular, low grade fever occasionally reaching 101° F. rectally.

Haemoglobin was 60% (8·8 g.); leucocytes 10,200 c.mm. (30% neutrophils, 65% lymphocytes).

Urine analysis showed albuminuria, and Benedict's solution was reduced equivalent to 0·5% glucose. The deposit showed a number of granular casts. Tests for urinary ketones were negative. The reducing substance was not fermented by yeast. Tauber's test for pentoses was negative, but Tollen's phloroglucinol test with spectroscopic examination suggested the presence of galactose. Confirmation was obtained by chromatography (see Appendix) of the urine.

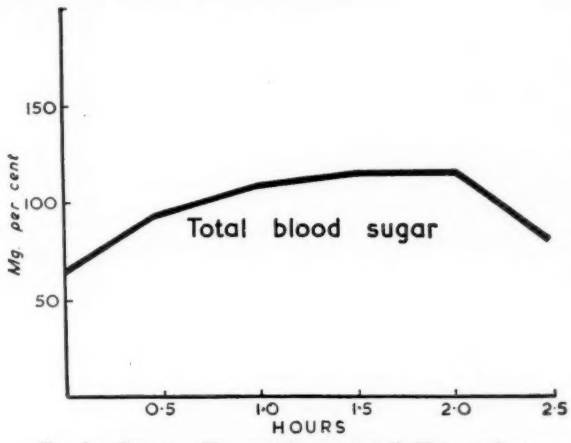

FIG. 2.—Case 1. Glucose tolerance test (1·75 g. per kg.).

An oral glucose tolerance test (Fig. 2) showed that fasting blood glucose was 65 mg.%, and after oral administration of 14 g. glucose, a maximum rise to 110 mg.% occurred at one and a half hours, falling to 80 mg.% at two and a half hours.

A galactose tolerance test (Fig. 3) gave a result typical

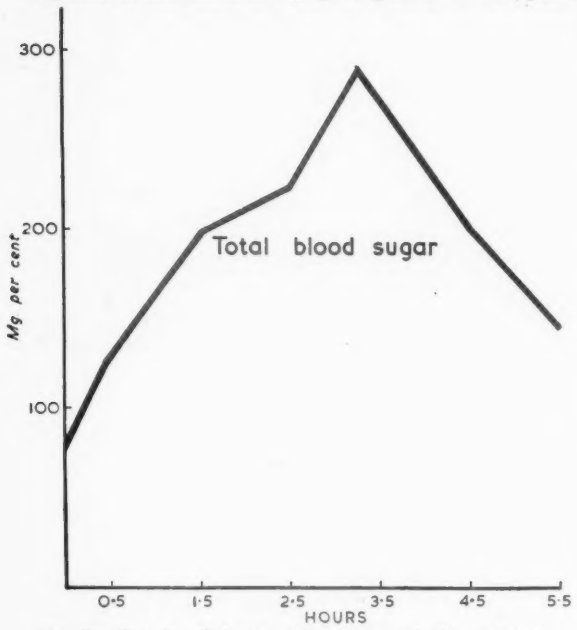

FIG. 3.—Case 1. Galactose tolerance test (1·75 g. per kg.)

of galactosaemia, the total blood sugar rising to a maximum of 265 mg. % at three and a half hours, and even at five and a half hours a value of 170 mg. % was found.

Liver function tests gave the following results:

June 26, 1951	Serum bilirubin	0·1	mg. %
	Alkaline phosphatase	37	KA units
	Thymol turbidity	3	units
August 9, 1951	Serum bilirubin	0·2	mg. %
	Alkaline phosphatase	18	KA units
	Thymol turbidity	1	unit
	Serum proteins	6·3	g. %
	albumin	4·4	g. %
	globulin	1·9	g. %

A liver biopsy (Figs. 4, 5) was taken. The surgeon described the liver as considerably enlarged and firm, with a finely granular surface.

Microscopical examination was reported as follows:

> 'There is a diffuse fibrosis involving portal areas, and bands of cellular fibrous tissue forming a continuous network throughout the liver. The portal veins appear to be involved and there is a slight fibroblastic proliferation around some of the centrilobular veins. The fibrous tissue shows slight diffuse infiltration by lymphocytes and there is an occasional focal collection of these cells. The liver parenchymal cells are swollen and their cytoplasm shows a finely vacuolated appearance, while some are distended by a clear vacuole. The latter do not show a definite zonal distribution, but are scattered in single cells or groups in a haphazard manner throughout the lobules.
>
> 'With fat stains the liver cells show fine sudanophil droplets and some show large globules. Glycogen is also demonstrated.'

An x-ray examination of the skull, long bones and abdomen showed no abnormality. Translucent areas were noted in the necks of the fourth and fifth right ribs and in the third and fourth left ribs.

FIG. 4.—Liver biopsy, Case 1: low power view.

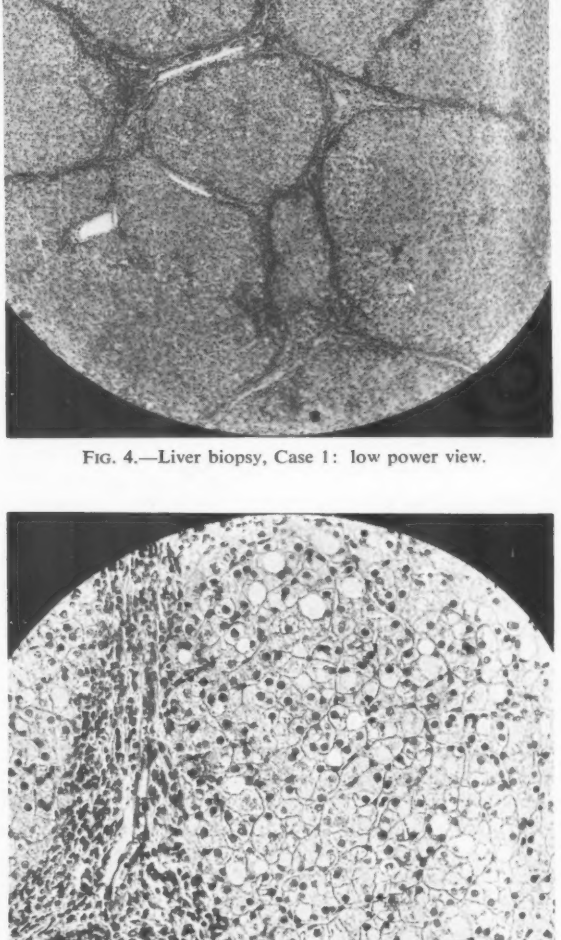

FIG. 5.—Liver biopsy, Case 1: high power view.

The blood cholesterol level was 55 mg. %. The Wassermann and Kahn tests were negative. The bone marrow was normal, with no cystinosis.

A lactose-free diet was constructed, using a soya bean preparation, a protein hydrolysate, and arachis oil, together with lactose-free solids. Powdered glucose was later added.

Considerable difficulty was experienced in getting the child to take much of this diet, although his mother gave him most of his feeds, and his weight fell by 11 oz. There was troublesome vomiting at times, but when seen one month after discharge from hospital his mother had been more successful in persuading him to take the diet and he had gained 2 lb. 1 oz. His general condition had improved, and he seemed altogether more lively, was able to sit up and had cut three further teeth. He seemed able to follow objects more easily, although it was difficult to detect any difference in the appearance of the cataracts. The liver clinically was unchanged, but a new finding was that the tip of the spleen was now palpable.

On December 8 we received the following report from Dr. George:

'Richard T. is now 17½ months old. He recently had a cold but seems to have got over that very well. He takes an intelligent interest in his surroundings and his manner is bright. He utters monosyllables, and has little accomplishments in which he seems to take a pride, e.g. "Clap hands till Daddy comes home", and others. He is unable to sit up without help, but when placed in a sitting position, maintains it and plays happily. He is able to stand by catching hold of furniture if first placed in the standing position. His appetite is good and he is taking a mixed diet. I understand his motions have been rather loose since coming from Llandough Hospital, but they have now become more formed and normal in appearance.

On examination, both fontanelles were closed. A large cataract is still present in the right eye but it is possibly less opaque than formerly. There is, however, room for two opinions about this. The child is able to see with at least one eye and picks up articles without hesitation. He has four incisor teeth in both the upper and the lower jaws.

His abdomen is considerably less protuberant than formerly. The liver can be felt one and a half to two fingerbreadths below the right costal margin. It is not as firm as formerly. He has a hydrococoele of the right spermatic cord.

There is no albumin, reducing substance or acetone in the urine.

On September 1, 1951, he weighed 17 lb. 14 oz. and today 23 lb.

This child has made a considerable advance since his condition was recognized last July. While still backward, he is no longer the apathetic child that he was then. It is difficult to be sure about the state of the cataract, but it is my impression that, on the periphery, at least, it is not so opaque as formerly. The liver has diminished in size very considerably. It formerly extended some four fingerbreadths below the right costal margin.'

Case 2. Raymond R., 12 days old, was admitted to the Port Talbot Hospital on account of jaundice of three days' duration. He was the firstborn of healthy parents. Delivery at term was normal and the pregnancy had been uncomplicated. The birth weight was 7 lb. and the feeds were of breast milk. There was no family history of hereditary or metabolic disorders.

He was a somewhat inert infant with normal tissue tone. There had been no vomiting or diarrhoea. The skin and sclera were slightly icteric. No abnormal dryness of the skin was observed and there were no cutaneous haemangiomata. Both breasts showed 'mastitis neonatorum'. He weighed 6 lb. 7 oz. The temperature and respiratory rate were normal. The abdomen was slightly distended but no prominent superficial veins were seen. The liver, the edge of which was palpable 6 cm. below the costal margin, was smooth in outline and firm (Fig. 6). The spleen was 2 cm. below the costal margin. There was no evidence of ascites and no other abnormal organs or masses were palpable. No abnormal physical signs were detected in the heart, lungs or central nervous system.

FIG. 6.

In both eyes the lenses appeared hazy (Fig. 7).

Movements of the eyes were normal in all directions, and they were attracted by lights from all quadrants. The tension of each eye was normal to finger pressure. Pupil reflexes were normal to light and well sustained. The lenses showed general clouding with increased opacity through the posterior cortex of each. The appearance suggested 'intumescence' of the lenses. There were no discrete opacities. Fundi were not clearly seen owing to lens changes, but appeared normal.

The urine was opalescent and of a colour reminiscent of lemon cheese. It gave a strong reduction of Benedict's solution and this, and the physical signs, suggested the diagnosis of galactosaemia.

During the subsequent days when investigations were proceeding, breast feeding was continued, but weight loss was progressive and there was an increase in the jaundice associated with greater apathy and inertness. On the seventh day after admission the

laboratory reported that the reducing substance in the urine was galactose. Breast feeds were therefore discontinued and a formula of 1½ oz. of calcium caseinate, 2 oz. of glucose and ¾ oz. of arachis oil was used. Later a supply of ' nutramigen ' was obtained.

The infant's weight was now 5 lb. 12 oz. and he was wasted.

Hartmann solution, 100 ml., followed by 90 ml. of whole blood were given by scalp vein transfusion with improvement in general condition and increased vigour in feeding.

Urine specimens consistently showed a negative Benedict's test (Fig. 8) on the formula feed. On breast

FIG. 7.—Case 2, R.R., aged 3 weeks, showing haziness of lenses.

feeding urine analysis showed that albumin was present and the *p*H 5·5. Benedict's test was strongly positive. Rothera's and Gerhardt's tests were negative. Tests for bile salts and bile pigments were respectively negative and positive. There was no increase in urobilinogen. Total sugar was 0·8 g. %. Rubner's and Bial's tests were negative. Barfoed's test for monosaccharides was positive as was the mucic acid test.

A centrifugalized deposit showed epithelial cells and granular casts, but no bacterial growth after 18 hours' incubation.

Phenylosazone crystals were identical in appearance and melting point with those prepared from a sample of galactose.

Serum protein analysis gave total proteins 7 g. % (albumin 4 g. %, globulin 3 g. %) A : G ratio 1·3 : 1.

Serum alkaline phosphatase was 30 units. A cephalin flocculation test was positive. A serum colloidal gold test gave 00000 and thymol turbidity 3 units. There were 3,400,000 red blood cells per c.mm. Red cells showed some macrocytosis with accompanying anisocytosis. The blood group was AII rr. Haemoglobin was 80% (Haldane), and the colour index 1·18. Leucocytes were 5,600 (polymorphs 50%, lymphocytes 45%, eosinophils 5%). Fasting blood sugar was 190 mg. %. The direct Coombs test was negative. The direct van den Bergh test formed a deep wine colour immediately. The indirect reaction gave a serum bilirubin level of 3·6 mg. %.

The Wassermann and Kahn reactions were negative. A galactose tolerance test (1·75 g. body weight), showed the abnormal values recorded in Fig. 9.

Radiographs of the skull, ribs and bones of the extremities did not show any abnormality.

Paper chromatography (see Appendix) showed a considerable excretion of galactose as demonstrated in 100 ml. of the urine.

Examination of the parents showed no change in their blood or urine and both had normal galactose tolerance

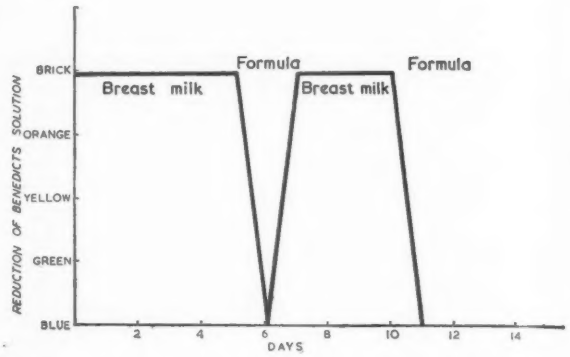

FIG. 8.—Case 2. Effect of diet on urinary reducing substance.

curves. It was noted that the parents of this case were natives of the same township as Case 1, but careful enquiry showed no known relationship.

Case 3. Hilda J., aged 7 years, was referred from a residential school for blind children for investigation of abdominal enlargement. Full details of her previous medical and family history were not available, but the following facts are known.

She was one of twins; her sister died soon after birth from an undetermined cause. Bilateral cataracts were found at an early age, and in spite of several operations vision remained poor. Physical growth

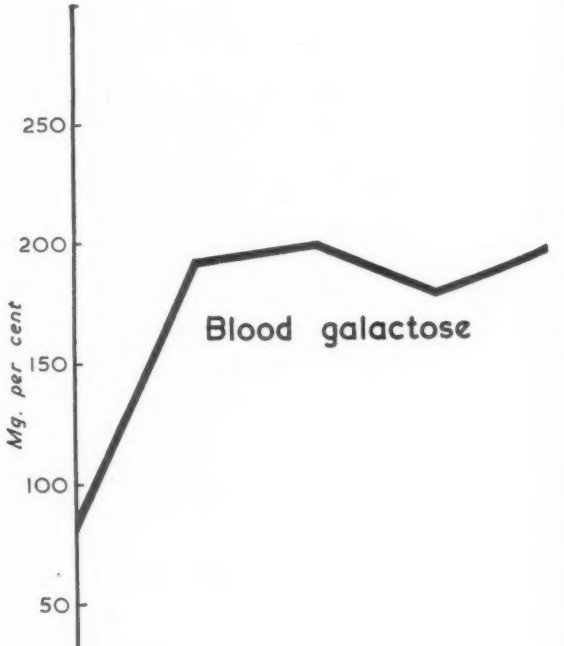

FIG. 9.—Case 2. Galactose tolerance test (1·75 g. per kg.).

and mental development were also retarded. The liver was found to be moderately enlarged and firm, the lower edge reaching midway to the umbilicus. No splenomegaly or ascites was found. On an ordinary diet containing a pint of cow's milk daily no reducing substance was found in the urine. A galactose tolerance test, however, showed hypergalactosaemia and galactosuria indicating impaired liver metabolism of galactose. Glucose tolerance was normal. Other liver function tests showed no abnormality.

The brief summary of this case is included in this report because, although it is incomplete, it suggests that a review of children in residential schools for the blind might reveal further cases.

Review of the Literature

Von Reuss (1908) published the first recorded case of galactosaemia in a marasmic infant with melituria; an enlarged cirrhotic liver was also found. Göppert (1917) reported a case in a child aged 4 years; three siblings had a suggestive history, but the diagnosis of galactosaemia was never established. Fanconi (1933) described a case of galactose intolerance in a 9-year-old boy, but hepatomegaly and cataracts were not present. In the case reported by Unshelm (1934) galactosaemia and liver enlargement returned to normal after galactose was withdrawn from the diet. Mason and Turner (1935) studied the case of a male negro infant with galactosuria, malnutrition, hepatosplenomegaly and evidence of impaired hepatic and renal function. Cataracts developed later. A follow-up of this patient to the age of 18 years is quoted in the paper by Townsend, Mason and Strong (1951). As the child grew older the galactose tolerance increased somewhat and no evidence of permanent liver disease was found, but he remained educationally subnormal (I.Q. 64).

The case described by Norman and Fashena (1943) resembled Unshelm's in that a galactose-free diet caused galactosaemia to disappear and liver function returned to normal. A similar case was recorded by Mellinkoff, Roth and MacLaggan (1945).

Detailed studies of carbohydrate metabolism in a case of galactosaemia are recorded by Bruck and Rapoport (1945). These authors emphasized the reciprocal relationship of galactose and glucose. Greenman and Rathbun (1948) also noted this, and found that the tolerance to galactose could be improved by adding glucose to the diet.

Goldbloom and Brickman (1946) reported two typical cases. In one of their cases, and in the patient described by Goldstein and Ennis (1948), lamellar cataracts showed signs of clearing after persisting for months on a galactose-free regime.

Liver biopsy in a case of galactosaemia was first described by Bell, Davidson and Scarborough (1950). The histological features were early fibrotic changes, focal cellular necrosis, and many liver cells distended by a single large lipid vacuole.

Donnell and Lann (1951) present four additional cases; three occurred in one family, though in two of these the diagnosis was not suspected before death, and galactose was not certainly identified. In one case portal cirrhosis and fatty infiltration of the liver was found at necropsy.

DuShane and Hartman (1951) report another case diagnosed at $4\frac{1}{2}$ months, and treated by eliminating milk from the diet and substituting a soya bean preparation. At the age of 24 months the infant appeared normal.

Townsend *et al.* (1951) present five additional cases and a follow-up of Mason's original patient. Liver biopsy in one patient showed a typical picture of Laennec's cirrhosis. These authors emphasize mental retardation as a salient complication of galactosaemia and the potential reversibility of the liver cirrhosis.

Gorter (1951) described three cases in a sibship of four, and quotes de Haas as having observed a family of 10 children of whom four had galactosuria. Gorter considers the disease to be an inborn error of metabolism of galactose, and states that symptoms are due to the toxic effect of galactose on the liver and kidney.

Discussion

Galactose, a dextro-rotatory stereo-isomer of glucose, occurs in nature as a constituent of lactose, and in certain complex lipids and proteins. Lactose, a β-galactoside in composition, occurs in the milk of mammals and is synthesized in the mammary gland. After ingestion lactose is hydrolyzed in the intestinal tract to glucose and galactose. The absorbed galactose is converted to glycogen by the liver. According to Bell, Davidson and Scarborough (1950) and Bridge and Mulholland (1951) the galactose is first converted to glucose by way of phosphorylated derivatives, and then to glycogen. Mason and Andersen (1941), discussing one form of glycogen storage disease, state that the liver in that condition is unable to convert glycogen to glucose or glucose to glycogen, but that a slow accumulation of hepatic glycogen results from the conversion of dietary galactose.

Where liver function is impaired, galactose is imperfectly metabolized, and after ingestion hypergalactosaemia and galactosuria occur. These findings are utilized in the galactose tolerance test for liver disease (Maclagan, 1940). Alimentary galactosuria is said to occur in normal infants after excessive ingestion of lactose (Rapoport, 1950). (See Appendix.)

The condition termed 'galactosaemia', on the other hand, is considered to be an inherent defect of carbohydrate metabolism in which the liver is unable to metabolize galactose. It has been placed among the 'inborn errors of metabolism' (Taggart and Mason, 1950), and Donnell and Lann (1951) refer to the likelihood of a specific gene, necessary for the metabolism of galactose, being absent or altered in this disease. A familial incidence has been reported on several occasions (Bell, Blair, Lindsay and Watson, 1950; Donnell and Lann, 1951; Gorter, 1951).

In most of the reported cases the neonatal course of the infant has been a stormy one, characterized by feeding difficulties, jaundice and failure to gain weight. Albuminuria and melituria are present. The reducing substance may vary in amount from day to day, depending on the diet, and identification may be very difficult. Galactose reduces Benedict's solution, but is not ordinarily fermented by yeast, though many samples of brewer's yeast will ferment it. Barfoed's test will show the reducing substance to be a monosaccharide, and Bial's and Tauber's tests will eliminate pentose. A positive mucic acid test will show that the sugar is either lactose or galactose, and the Rubner test can be used to eliminate the former. Tollen's phloroglucinol reaction and the preparation of galactose osazone confirm the occurrence of galactosuria. In Case 2, a breast-fed infant, identification of galactosuria was definite using the above tests. A breast-fed baby taking 600 g. milk, receives about 22·5 g. of galactose per day. In Case 1, the relative proportion of dietary galactose was much less, and the galactosuria less constant and profuse. In both these cases the diagnostic help afforded by chromatography was great. In Case 3 no spontaneous galactosuria was observed, but oral administration of galactose produced hypergalactosaemia and galactosuria. This patient resembles that of Fanconi (1933), and Mason and Turner's patient when seen at 7 years old, who could tolerate 200 ml. milk at each meal without melituria.

Much interest has been shown in the liver enlargement constantly present in this disease. Abnormal liver function tests are an unusual finding in the reported cases. Cases 1 and 2 showed a high phosphatase level, and in Case 2 hyperbilirubinaemia was also present.

Biopsy studies are recorded by Bell *et al.* (1950) and by Townsend, Bell, *et al.* (1951). In the former histological examination showed many hepatic cells distended by a single large lipid vacuole, focal cellular necrosis and early fibrotic changes. The authors considered infiltration with fat to be the basic cause of the liver enlargement. In Townsend's case liver biopsy showed typical Laennec's cirrhosis. There was no vacuolation within the hepatic cells. Cirrhosis of the liver was found at necropsy in four other cases of galactosaemia.

Liver biopsy in Case 1 (Figs. 2, 3), the third to be reported, shows features of both the previously described cases. Diffuse hepatic fibrosis is present, the appearance closely resembling that of Townsend's case, and fatty changes are also prominent.

The cause of the hepatic cirrhosis is uncertain. Mason and Turner (1935) thought it might be due to hypoglucosaemia; the more likely explanation is a direct toxic action of galactose.

A curious feature of all the proved cases of galactosaemia is the absence of ketosis, which occurs commonly in glycogen storage disease and in conditions associated with fatty cirrhotic livers. Possible explanations are the normal liver glycogen, or the toxic action of galactose preventing the formation of ketone bodies.

Cataracts have been reported in nine cases of galactosaemia. In three cases they disappeared after the child had been on a galactose-free diet, though taking several months to do so. In two other cases the opacities became less, and no improvement occurred in the remainder.

Mitchell and Dodge (1935) and Yudkin and Arnold (1935) described cataracts as occurring fairly constantly in young rats fed on a diet in which the main carbohydrate was lactose or galactose. The cause of the cataracts is still obscure. Bellows and Rosner (1938) noted a decrease in the permeability of the lens capsule preceding the formation of cataracts, and Bellows and Chinn (1941) produced cataracts in young animals within a few minutes of an intravenous injection of hypertonic galactose solution. These authors suggest an upset in osmotic balance in the lens, together with alterations in the permeability of the lens capsule, as responsible for the formation of galactose cataracts. Weekers (1943) stated that hypocalcaemia was necessary for galactose cataracts to develop. An interesting observation recorded by Bannon, Higginbottom, McConnell and Kaan (1945) was that galactose cataracts produced in embryos affected only the nucleus of the lens, the actively growing regions remaining unaffected. Well-developed cataracts were present in Cases 1 and 3; in Case 2 the lenses showed a diffuse haziness, described as 'intumescence'. The earliest reported cataract was in Bruck and Rapoport's patient aged 7 weeks.

The nomenclature of the disease may, with advantage, be revised; that at present in use is open to various objections. The term commonly

used, ' galactosaemia ', like ' uraemia ' and ' hyperglycaemia ' connotes a particular finding in the blood which may occur in a number of diseases. ' Galactose diabetes ' on the other hand suggests too close an analogy with diabetes mellitus, unsupported by the pathogenesis of the disease. If it is accepted that the condition is an inborn error of metabolism, then to bring it into line with the other conditions in that group, the term ' essential galactosuria ' or ' congenital galactosuria ' would be preferable. Further, if it were agreed that damage to the eyes, liver and kidney resulted from toxic action of the galactose, then an analogy with the de Toni-Fanconi syndrome becomes apparent, and the most suitable name for the condition would be either ' galactose disease ' or ' galactosis '.

Summary and Conclusions

Two cases of galactosaemia in infants are presented, and a third case of probable galactosaemia in a 7-year-old girl with cataracts, liver enlargement and galactose intolerance.

The importance of early diagnosis is emphasized by the improvement shown in Case 2 when the infant was placed on a lactose-free diet.

The diagnostic help given by chromatography is demonstrated.

The results of liver biopsy are described, the findings being intermediate between the only two previously reported biopsy studies.

It is suggested that the name of the disease be ' galactosis '.

We gratefully acknowledge the help we have received from Dr. H. Bickel, of the Biochemical Department of the Children's Hospital, Birmingham, both in providing us with the report on chromatography and in giving his diagnostic help.

To Mr. Foster who performed the liver biopsy, to Dr. Richards who reported on the sections and to Mr. Rupert Parry and Mr. Hibberd who gave us reports on the eyes, we express gratitude for their valuable assistance. We offer thanks to Dr. George for his interesting comment on Richard T., also Mr. Salter and Mr. Bennett for technical assistance. Finally, our thanks are due to Mr. Napper and Mr. Griffiths for supplying the photographs.

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Addendum

When last seen on April 27, 1952, Richard T. was considerably improved and was gaining weight, talking and walking. The cataracts showed little, if any, change.

On July 10, 1952, Raymond R. was described by his mother as a normal child, and was making excellent progress. Both children have been kept on a lactose-free diet.

APPENDIX

PAPER CHROMATOGRAPHIC INVESTIGATIONS ON THE URINE OF PATIENTS R.T. AND R.R.

BY

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Technique

Sugar Chromatography. The urine specimens were preserved with thymol and arrived in good condition. The technique employed was that described by Partridge and Westall (1948), and by Horrocks and Manning (1949). The chromatograms were one-dimensional butanol-ethanol-ammonia runs, the developer aniline phthalate. The volume pipetted at the base of each column was 50 μl. for Richard T., 10 μl. for R.R., 50 or 100 μl. for the normal controls.

Amino-acid Chromatography. The technique employed was that of Consden, Gordon and Martin (1944), of Dent (1947 and 1948), and of Hermann, Bickel and Fanconi (1949). The urine specimens were de-proteinized by passing them through a collodion sac (Greenberg and Gunther, 1930) to remove albumin, and if necessary, de-salted (Consden *et al.*, 1947). For each urine chromatogram the quantity of urine used contained 500 μg. nitrogen. All the chromatograms were two-dimensional phenol-collidine-lutidine runs and were treated with perhydrol. After developing the papers with ninhydrin the colour intensity of the spots is expressed either in figures—1 for the weakest and 10 for the strongest—or compared with test spots of pure taurine placed above the urine spot in five different positions and concentrations (5-10-20-40-60 μg. of taurine) before the run is started.

Results

Sugar Chromatography. The sugar chromatograms of the patients Richard T. and R.R. showed a definite galactosuria as demonstrated by the strongly coloured spots in the runs of their urine (Fig. 1, column 3, Fig. 2, columns 2, 3, 4, 6). The position of these spots is identical with that of pure galactose, which was run in Fig. 1 in columns 1 and 6, in Fig. 2 in columns 1 and 7 together with several other pure sugars. Normal urine (Fig. 1, column 7, Fig. 2, column 5) does not give any colour reaction with aniline phthalate, even when volumes of 200 μl. are used. This point has been established by a chromatographic study of the urine of 100 school children and 30 infants from the age of 1 month onward. Fig. 3 shows the sugar chromatograms with the urines of Richard T. and a normal control child during three days' lactose ingestion. The normal child excreted traces of lactose in the urine on the first and last lactose day, but no other sugars, and, in particular, no galactose. Richard T. did not excrete any sugars during the first two lactose days, but a definite galactosuria developed on the third lactose day.

Amino-acid Chromatography. Glycine and serine are the only amino-acids of sufficient concentration to give a colour reaction with the ninhydrin spray. More than 200 urines of children of all ages were tested by the authors (unpublished data) to establish the chromatographic pattern and spot intensity in healthy children. None of the normals, with the exception of newborns, exhibited an amino-aciduria comparable with that of

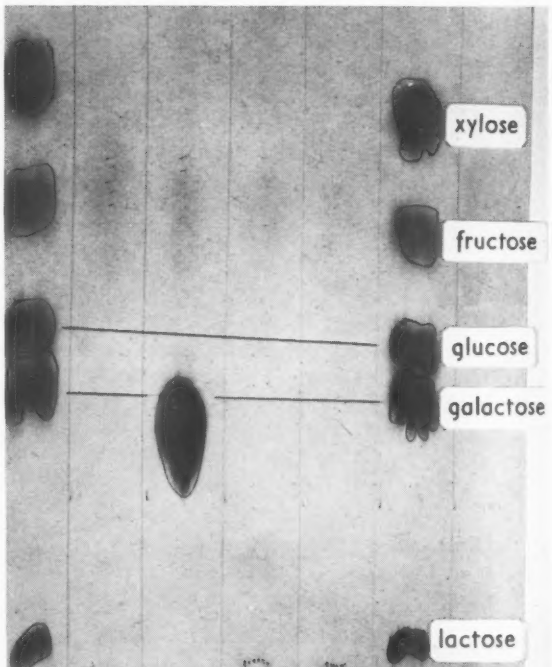

FIG. 1.—One-dimensional sugar chromatogram from 100 μg. each of pure lactose, galactose, glucose, fructose and xylose (columns 1 and 6); 50-200 μl. normal urines (columns 2, 4, 5 and 7); 50μl. urine of Richard T., of June 30, 1951 (column 3). Benedict's test green-yellow.

Richard T. and R.R. A normal urine of a volume containing 500 μg. nitrogen rarely shows more than three to six faint amino-acid spots, generally glycine, alanine, glutamine, glutamic acid, sometimes traces of histidine, cystine and, still more rarely, serine, taurine and β-amino-isobutyric acid. Richard T., on the contrary, showed a marked amino-aciduria; glycine, serine, alanine, glutamine were excreted in excess, but still more pathological was the excretion of amino-acids not occurring in normal urine, such as threonine, valine and the leucines.

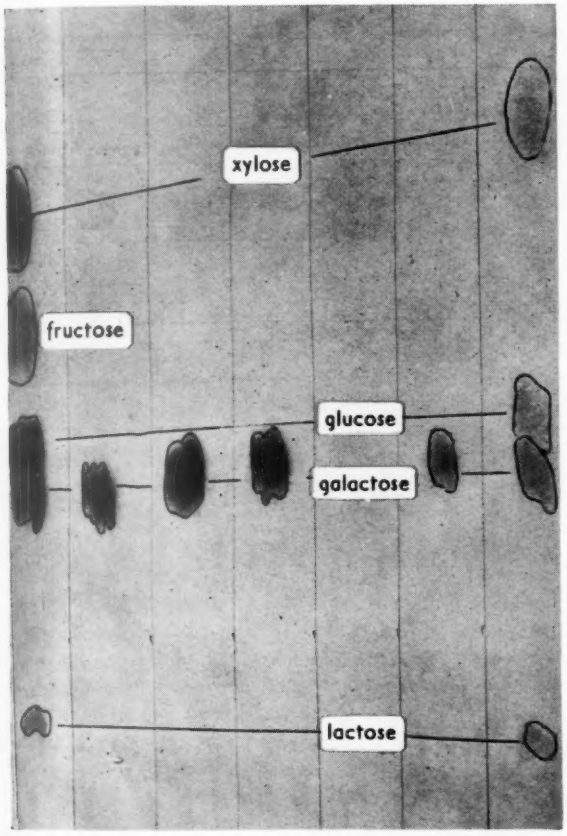

FIG. 2.—One-dimensional sugar chromatogram from pure sugars (column 1 and 7); 100 μl. of normal urine (column 5); 10 μl. urine of R.R. on different days (columns 2, 3, 4 and 6). Benedict test on urines in columns 2, 3 and 4 green-yellow; in column 6 green.

Chromatograms with other urine specimens of this patient showed in addition an increased excretion of lysine, methionine, phenylalanine, tyrosine and cystine (as cysteic acid). R.R.'s urine chromatograms also showed an increased output of various amino-acids, especially of glycine, serine, taurine, threonine, cystine, proline and methionine. The last two are rarely found together even in pathological urines.

Discussion

Paper chromatography provides an excellent and comparatively simple method of testing urine, plasma and other biological fluids for their sugar and amino-acid composition. Chromatography has the great advantage of being highly sensitive and specific; its main disadvantage is its semiquantitative nature. Sugar chromatograms on the two patients showed a definite galactosuria. Galactose excretion could be demonstrated even when Benedict's reduction test gave an indefinite blue-green or green colour reaction. Chromatography is thus superior to the Benedict test, as it is both more specific and more sensitive, and may reveal a galactosuria which could easily escape the usual Benedict test.

The demonstration of amino-aciduria in both patients is a finding which, to our knowledge, has so far not yet been mentioned in the literature on galactosaemia. Up to 15 amino-acids were excreted in excess. The pattern of the amino-acid chromatograms was similar to that seen in the urine of some patients suffering from liver diseases, such as cirrhosis and atrophy of the liver. The amino-aciduria continues even when the galactosuria has ceased as a result of a galactose-free diet. This was observed in a patient of Dr. Snyder, New Orleans, who kindly sent us a urine specimen for chromatographic investigations.

Unfortunately we have so far had no opportunity of studying the amino-acid plasma level in galactosaemia so that the mechanism of the amino-aciduria in this disease, whether over-flow or lowered renal threshold,

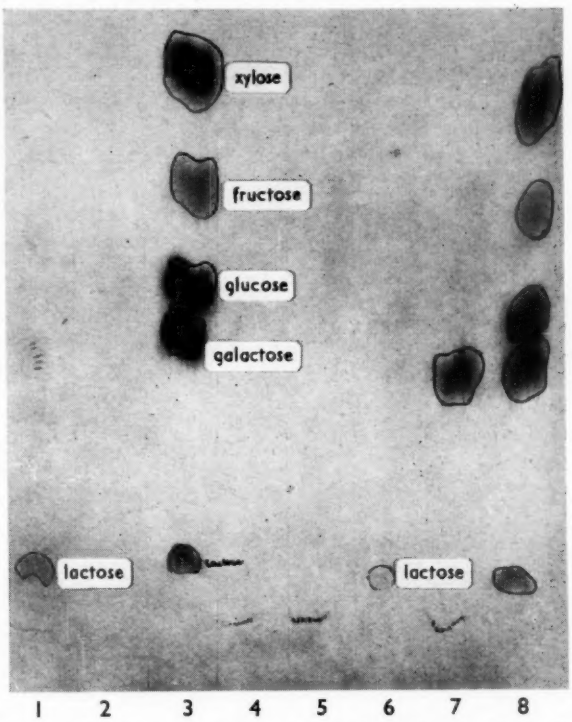

FIG. 3.—One-dimensional sugar chromatogram showing the results of lactose feeding on the urines of Richard T., first day, July 6, 1951 (column 2), second day (column 5), third day (column 7); normal control, first day, July 6, 1951 (column 1), second day (column 4), third day (column 6). Chromatograms of 100 μg. of pure sugars are shown in columns 3 and 8.

cannot be assessed. The well-known fact that the liver of galactosaemic patients is damaged (Bell, Blair, Lindsay and Watson, 1950), may lead one to suspect that this is the cause of the amino-aciduria. Parenchymal damage of the liver, however, does not always lead to amino-aciduria, even in advanced stages with considerable liver destruction. We have seen moribund patients suffering from liver cirrhosis without amino-aciduria. Furthermore, the albuminuria in galactosaemia points to a kidney lesion in this disease. Our tentative conclusion is that the amino-aciduria in galactosaemia is due either to the failure of a specific liver function essential to the amino-acid metabolism or to a disturbance of the reabsorption of certain amino-acids in the kidney in addition to the metabolic error in galactose utilization by the liver.

Summary

Paper chromatographic studies on two patients suffering from galactosaemia revealed, besides galactose, a pathological excretion of various amino-acids in the urine.

Galactosuria may be demonstrated by chromatography even where the galactose concentration is too weak for a positive Benedict test.

The amino-aciduria persists after cessation of the galactosuria following a galactose-free diet.

The pattern of the amino-aciduria is similar to that in other cases of liver damage. A kidney lesion as a possible cause of the amino-aciduria has, however, also to be taken into account. Future investigations into the plasma level of the various amino-acids may reveal the mechanism of the amino-aciduria.

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POLYOSTOTIC FIBROUS DYSPLASIA

BY

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Polyostotic fibrous dysplasia is a disease that deserves to be better known for it is more frequent than is generally appreciated. Von Recklinghausen's (1891) description of what appear to be two examples of this disease together with one of hyperparathyroidism seems to have set a precedent for many fruitless parathyroid explorations. This has occurred despite Hunter and Turnbull's (1931) differentiation of 'osteitis fibrosa in multiple foci' from 'osteitis fibrosa cystica generalisata'.

Interest in the condition and a recognition of the frequent association with other features was aroused by Albright, Butler, Hampton and Smith (1937) in a paper describing a syndrome of disseminated osteitis fibrosa, skin pigmentation, and, in females, sexual precocity. Despite earlier descriptions by McCune and Bruch (1937) and Weil (1922) this syndrome has often been called Albright's syndrome.

Lichtenstein (1938) in a review and pathological report suggested the term polyostotic fibrous dysplasia. In his view the bony lesion is the one essential feature of the disease.

Three patients with this disease have been seen in The Hospital for Sick Children, since 1938. One was reported by Warrick (1949) and is referred to by Jolly (1951). This was a boy who showed skin pigmentation, involvement of the skull and probably two ribs, and sexual and skeletal precocity. His parents and his four siblings showed no skin pigmentation. The other two are reported in this paper for the first time.

Case Reports

Case 1. J.F., a boy aged 6 when first admitted to this hospital on June 30, 1946, was referred to Dr. Pearson on account of bone cysts. These had been discovered when he sustained a pathological fracture of the right humerus in October, 1945. Further fractures of the right humerus and right radius had occurred during treatment in a plaster cast, but all had healed well. Before these events he had always been well. He was re-admitted on several further occasions with pathological fractures.

He had three siblings, one of whom, an elder sister, showed two *café au lait* patches on the right thigh. His mother had a small, faint *café au lait* patch over the left cubital fossa. Her only sister showed no pigmentation. The boy's father showed none and it was said that the father's nine siblings showed none. The boy's maternal grandmother had a small, faint *café au lait* patch on the left arm. His maternal grandfather was said to be free of these spots, but had a sister who had a small, dark *café au lait* patch on the abdomen; there were five other siblings in this family. The patient's mother had no x-ray evidence of bone disease in the left arm and his sister with pigmentation had no lesions of the skeleton on x-ray.

Examination in January, 1948, showed a thin, alert boy with a bony swelling on the upper and outer side of the right forearm, a palpably enlarged right humerus and slight limitation of supination on that side. The tonsils and tonsillar glands were enlarged. No abnormality was found on clinical examination of other bones, heart, lungs, abdomen, genitalia, nervous system or neck. A small *café au lait* patch was present on the lower right abdominal wall.

Radiographs showed diffuse involvement of the humeri (Fig. 1) which were expanded, the cortex thinned in places, and the normal structure replaced by translucent and 'ground glass' areas. Similar cystic appearances were seen in both radii, several metacarpals and phalanges in both hands, in the eleventh right rib and the right femur and tibia. The skull was normal. The bone age remained normal. There was no generalized osteoporosis. Some progression of the lesions occurred during the period of observation. An intravenous pyelogram showed no abnormality.

A biopsy from the right humerus showed replacement of the marrow spaces by fibrous tissue.

FIG. 1.—Radiograph of right humerus of Case 1.

Examination of the urine showed absence of protein and Bence-Jones protein on several occasions.

Biochemical investigations gave a blood calcium level of 10·4, 10·2, 9·7, 9·4 mg. per 100 ml.; inorganic serum phosphorus, 3·6, 3·8, 3·4, 3·3 mg. per 100 ml.; serum alkaline phosphatase, 27·5, 32·7, 37·8, 45·8 units. Two four-day calcium balance periods showed a positive calcium balance of 0·44 g. a day and 0·34 g. a day respectively.

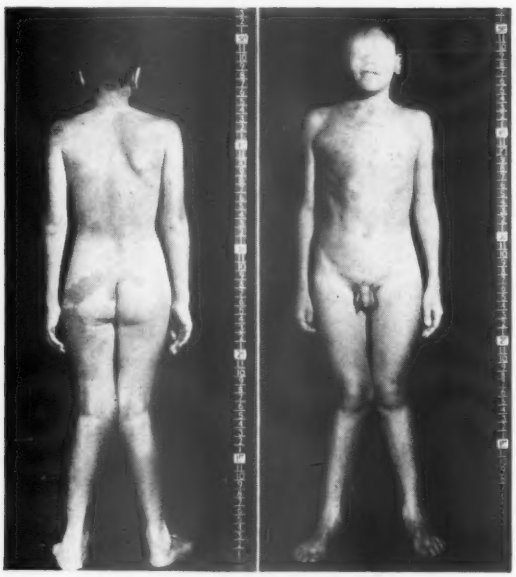
The blood urea, plasma proteins, blood count and blood sedimentation rate were normal.

Case 2. X.C., a 13-year-old boy of Greek parentage and Egyptian domicile, was sent from Cairo by Dr. Cardiacos to Dr. Lightwood and admitted on June 21, 1951, with bilateral knock knee. This had been noted when the boy was 6 years of age and had increased rapidly in the last three years. Areas of skin pigmentation had been present at birth. Puberty had not occurred unduly early.

Birth weight was 10 lb. and his early development normal. He had been jaundiced for a month when 6 years old, had Giardia dysentery when 7, and a transient left pleural effusion when aged 10.

The parents were healthy. His only sibling, a 3-year-old girl, had a small brown spot on the right thigh seen in a photograph. The paternal grandfather was reliably reported to have had brown pigmented areas of skin on the back and right thigh.

Examination showed an intelligent boy of average height and a little over average weight for his age (Figs. 2 and 3). The complexion was dark and on the face, neck, right thorax, buttocks and thighs there were extensive areas of brown pigmentation with irregular edges. A little straight pubic hair was present but no axillary or facial hair. The genitalia were normal for his age. The skull showed marked frontal and parietal bossing giving the 'hot cross bun' effect. There was facial asymmetry with prominence of the left forehead. The nasal bridge was flat and wide, the interpupillary distance being 171 mm. The upper limbs appeared normal apart from marked hyperextensibility of the metacarpophalangeal joints and an ability to do 'double-jointed' tricks by subluxating the right humerus at the shoulder joint. A mild lower dorsal kyphoscoliosis was present. The lower limbs showed bilateral genu valgum with seven inches intermalleolar separation. The thyroid isthmus was palpable. Detailed examination of vision and hearing only revealed some peripheral contraction of the visual fields, especially on the left with no other abnormality, nor was any abnormality found in the nervous system, heart, lungs or abdomen.



FIGS. 2. FIG. 3.
FIGS. 2 AND 3. Case 2.

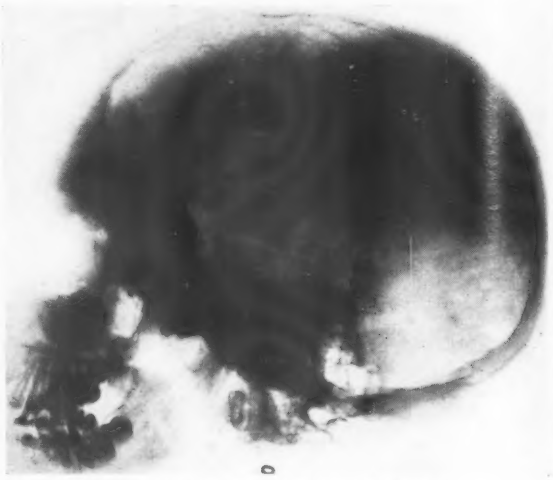


FIG. 4.—Radiograph of skull of Case 2.

Radiographs (Figs. 4 and 5) showed that the bone age was within normal limits. There were marked thickening and patchy sclerosis of the base of the skull, the maxillae, the frontal bones and in the parietal regions. The femora showed large translucent areas and in places there was expansion of the shaft and thinning of the cortex. Similar changes were present in all bones except the clavicles, carpus, some phalanges, most ribs, some vertebrae and several tarsal bones.

A skin biopsy showed that the epidermis was normal apart from excessive melanin pigmentation of the rete Malpighi. Van Gieson's stain was taken up abnormally by the deeper areas of dermal collagen, and there was mild perivascular infiltration with small round cells and histiocytes, some of the latter containing melanin granules. The vessels and elastic network of the dermis were normal.

Bone biopsy showed the typical features of osteitis fibrosa, that is, residual bone trabeculae embedded in dense fibrous tissue.

Biochemical investigations gave an inorganic serum phosphorus level of 3·1 mg. per 100 ml.; blood calcium of 11·2 mg. per 100 ml.; alkaline serum phosphatase of 84 units. Blood urea, chlorides and bicarbonate were normal.

Blood Wasserman and Kahn reactions and the Mantoux test 1 : 100 were negative. No protein or Bence-Jones protein was found in two specimens of urine. Amino-acid excretion was normal.

As it appeared likely that the bone disease was still active, stapling over the lower femoral epiphyses was carried out to ameliorate the knock knee. Later when activity will presumably be less, osteotomies may be required.

Discussion

Polyostotic fibrous dysplasia is a disease of childhood, the lesions becoming arrested in adult life. The sexes are equally affected. Attention is usually called to it by deformities, by pathological fracture, by pain, or less frequently, by the associated endocrine changes.

The Bony Lesion. One or many bones may be affected. Schlumberger (1946) considers it impossible to relate monostotic instances of fibrous dysplasia to the polyostotic form and believes the former follows bone injury. That some cases where one bone alone is affected do belong with the polyostotic group is perhaps supported by the concurrence of monostotic disease and pigmentation in the case of Dockerty, Ghormley, Kennedy and Pugh (1945), Jaffe's (1946) two cases, Russell and Chandler's (1950) two cases and the two cases of Strassburger, Garber and Hallock (1951). The disease tends to affect the bones developed from one limb bud or to be unilateral. The proximal long bones and the base of the skull are most often affected. Epiphyses are rarely involved and then only after fusion.

FIG. 5.—Radiograph of hand of Case 2. (Both hands showed a similar picture.)

Falconer, Cope and Robb-Smith (1942) think that the histology suggests 'the primary change is a marrow fibrosis with secondary absorption of the laminated trabeculae and then a new formation of fibre bone'.

Additional features are the frequent presence of cartilage islets, occasionally of small cystic spaces and of small collections of xanthoma cells and rarely of osteoclastomata (Dockerty *et al.*, 1945). Lichtenstein (1938) considers the presence of cartilage islets in the marrow fibrosis pathognomonic. Schlumberger (1946) has brought evidence to show that it is not and that it may be seen as part of the reparative process in bone after injury. Osteogenic sarcoma occurring in this disease has been reported by Coley and Stewart (1945, two examples), by Jaffe (1946) and by Snapper (quoted by Albright, 1947).

Radiologically the marrow fibrosis shows in thinning and expansion of the cortex of bones. Bending occurs and the 'shepherd's crook' deformity of the femur is typical. Normal bone pattern is lost, a 'ground glass' appearance replacing it together with dense trabeculae giving a cystic appearance. At the base of the skull involvement shows itself as dense sclerosis and overgrowth which may result in compression of cranial nerves.

Skin Pigmentation. *Café au lait* patches are seen in the majority of cases. There is some tendency for them to occur on the more affected side. Pigmentation has been reported on the buccal mucosa. Albright has repeatedly stressed the irregular margin of these areas and considers it a useful contrast with the smooth, regular-edged *café au lait* patches of neurofibromatosis. Histologically it is due to excessive melanin deposition, chiefly in the basal layer of the epidermis.

Endocrine Changes. The most frequent of these is skeletal precocity giving rapid early growth and eventual dwarfing. Less often there is sexual precocity which is common in females but rare in males (Lange, 1938; Falconer *et al.*, 1942; Warrick, 1949, two cases). The sexual precocity is of the true or 'cerebral' type. Thyroid enlargement is not uncommon and several examples of hyperthyroidism are reported. Acromegaloid features were present in the two patients of Falconer *et al.* (1942) and in that of Peck and Sage (1944), and

gynaecomastia has been seen by Moehlig and Schreiber (1940) and by Albright.

Chemistry. Calcium and phosphorus levels in the blood and calcium balances are normal. The only abnormality of blood chemistry is the frequent elevation of the alkaline serum phosphatase. In the urine Bence-Jones protein was found in the patient of Murray, Kirkpatrick and Forrai (1946) and in one of Albright's patients.

Aetiology. General opinion now inclines to consider this disease to be of congenital origin. Helfet (1940) and Uehlinger (1940) believed it might be due to chronic hyperparathyroidism. Bremer (1941) produced fibrous lesions in bone by giving oestrogens to experimental animals and thought this effect was produced through the parathyroids. Further evidence to support these ideas has not been brought forward and the often striking asymmetry of the lesions is a real difficulty in accepting them.

Four examples have been reported following neonatal jaundice (McCune and Bruch, 1937; Summerfeldt and Brown, 1939; Braid, 1939, two cases). Braid suggested that the condition might result from early liver damage, but there has been no more evidence to support this.

There has been no evidence that heredity plays any part. Hirsch (1929) reported three siblings with 'generalized hyperplastic malacia' and a history of 'spasms' in childhood. Particularly as he states that 'the cancellous structure is everywhere normal', I am unconvinced that these were examples of polyostotic fibrous dysplasia as Warrick (1949) suggests. However, in Cases 1 and 2 reported here there is a family history of skin pigmentation. The significance of this cannot be judged without knowing the incidence of such pigmentation in the population. To determine this 85 adults in the general medical wards of a London hospital and 15 children over the age of 5 were examined, in all 50 females and 50 males. A *café au lait* spot was defined as of developmental origin, faint to dark brown colour, being neither raised, palpable nor altering skin texture, and of at least 1 cm. diameter. Five females showed them and seven males. Having shown such a high incidence of *café au lait* spots in the population as 12%, the significance of the two family histories of pigmentation is doubtful.

Café au lait patches without other abnormality have been regarded by some as the *forme fruste* of neurofibromatosis. Taking this as a starting point Thannhauser (1944) has endeavoured to link neurofibromatosis with polyostotic fibrous dysplasia. Albright (1947) has defended the separateness of these entities. It would be of interest to determine whether the thickening and club-like expansion of the finest skin-nerves seen in the *café au lait* patches of neurofibromatosis (Stalmann, quoted by Thannhauser) is present in polyostotic fibrous dysplasia. There are no reports of this having been done.

Any explanation of the pathogenesis must account for the involvement of tissues from two germ layers present in three systems, and for the tendency to be unilateral. Albright and Reifenstein (1948) consider the lesion to be a disseminated neurological one, the sexual precocity being due to a hypothalamic lesion. Thannhauser's suggestion that the hypothalamus might be affected by overgrowth of bone at the base of the skull is difficult to maintain as not all examples with endocrine changes have shown skull involvement, radiologically at least.

Lichtenstein (1938) considers the bony lesion to be due to 'perverted activity of the specific bone-forming mesenchyme' and likens it to a hamartoma.

In an incomplete search of the literature, but covering some 140 cases with involvement of more than one bone, I have tried to discover the frequency of congenital abnormalities in this disease. If they were much increased there would be good evidence in support of a congenital origin.

Ten cases were found having associated congenital anomalies, namely: (1) mental retardation (Snapper and Parisel, 1933); (2) mental retardation, and at necropsy diminution in size of one mamillary body and an extra nucleus in the adjacent tissue (Albright, Butler, Hampton and Smith, 1937); (3) coarctation of the aorta and rudimentary left kidney (Coleman, 1939); (4) acyanotic congenital heart disease (Dockerty *et al.*, 1945); (5) congenital arteriovenous fistulae of left arm and leg (Stauffer, Arbuckle and Aegerter, 1941); (6) vascular and pigmented naevi (cited by Jaffe, 1946); (7) Meckel's diverticulum and patent foramen ovale (Sternberg and Joseph, 1942); (8) pseudoxanthoma elasticum (Upjohn, 1951); (9) osteopoikilosis (Osgood, 1946); and (10) multiple pigmented naevi (Behrend, 1945).

In assessing the significance of this group the factor of selection must be considered because of the more thorough examination such people undergo. Selection may also have occurred in that those showing congenital abnormalities are more likely to be reported. No comparable figures for the incidence of congenital anomalies are available,

* A case with heart disease reported by Murray *et. al.*, (1946) and the single cases with neurological lesions of Albright, Scoville and Sulkowitch (1938) and of Dockerty, *et al.* (1945) have not been included because of the possibility of non-congenital causation. Summerfeldt and Brown's (1939) case with an I.Q. of 70 must be included in the lower normal range.

the 2% figure commonly accepted being the figure found in surveys of infants in the first month of life. Of the ten instances listed only Nos. 4, 5 and 6 and 10 are likely to have been included in such a survey. That an increased incidence of congenital anomalies exists in this disease has, therefore, not been proven.

Differential Diagnosis. The following have to be considered.

HYPERPARATHYROIDISM. This may be differentiated by the pains and weakness of the patient, the generalized osteoporosis, high serum calcium and negative calcium balance.

NEUROFIBROMATOSIS. Papillomata, neurofibromata and few bony lesions tending to be located about the knee joint are shown.

PAGET'S DISEASE. Paget's disease occurs later in life and is a difficulty only when the skull alone is involved. Cortical thickening of bone occurs.

OLLIER'S DISEASE. This is recognized by the shortening and thickening of affected bones and by the frequent involvement of epiphyses.

EOSINOPHILIC GRANULOMA AND LIPOID RETICULOSIS. These conditions usually show more sharply punched-out lesions and differentiation may be difficult without a biopsy.

MELORHEOSTOSIS. Melorheostosis is differentiated by the presence of irregular cortical projections and the involvement of epiphyses.

Treatment and Prognosis. The expectation of life is usually not altered. In adult life progression of the lesions very rarely occurs though deformities and fractures may further complicate them. Fractures heal well. Treatment consists of the correction of deformities and the care of fractures. Though often unsuccessful, curettage and bone grafting sometimes give very good results.

Summary

The three instances of polyostotic fibrous dysplasia occurring at this hospital are reviewed and two of these are published for the first time. Both these new cases belong to families in which several members have *café au lait* spots. To determine the significance of this, 100 people were examined and 12 found to have one or more *café au lait* spots.

In view of this high incidence the significance of the family histories remains doubtful.

The condition is reviewed and current ideas of pathology and aetiology are discussed.

Ten cases with associated congenital abnormalities have been found in the literature. That this represents a high incidence of association has been shown to be unproven.

I wish to express my thanks to Dr. R. Lightwood for permission to publish his case and for his helpful criticism and to Dr. Cedric Carter for advice in the preparation of this paper.

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CYSTINOSIS

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The relationship between some cases of so-called renal rickets and disturbances of cystine metabolism was first suggested by Lignac (1924) who described the case of a 3-year-old boy dying with severe rickets and dwarfism. There was a preceding history of polyuria and glycosuria. Post-mortem examination revealed the presence of aggregations of cystine crystals throughout many organs particularly those of the reticulo-endothelial system and the kidneys. Lignac (1937, 1938) subsequently reported two very similar cases, in a boy of 2 years and a girl of 14 months. Cystine stones were discovered in the latter's renal tract as well as diffuse cystinosis of the body tissues. Details of these cases are shown in Table 1.

Russell and Barrie (1936) described two and possibly three further cases which are the only cases in the English literature. Their first was a girl who died at the age of 12 years having suffered from renal rickets since infancy. Glycosuria had been found repeatedly and had been shown to be renal. She eventually died from renal failure. The second was a boy dying at 16 years, also from renal failure, who had been treated in early childhood for rickets. In neither case was there enlargement of the liver or of the spleen. At necropsy cystine crystals were found throughout the reticulo-endothelial system and the kidneys showed glomerular destruction, tubular atrophy and interstitial fibrosis. A severe case of cystinosis was described by Beumer and Wepler (1937). This was a boy who died at 17 months of age from marasmus and rickets. During life hepatosplenomegaly had been noted as well as a renal type of glycosuria.

A most valuable contribution to the subject has been made by Hottinger and his colleagues in Basle (Hottinger, 1941; Roulet, 1941; Bürki, 1941; Esser, 1941; Freudenberg, 1941) who described a boy whom they followed from the age of 20 months to his death at 7½ years. He presented at first with rickets, dwarfism and a renal type of glycosuria. At the age of 7 years the liver and spleen were enlarged and the corneae were seen to be hazy. Slit lamp and later biopsy examination showed this to be due to the deposition of refractile cystine crystals in the cornea and conjunctiva. The diagnosis of cystinosis was further confirmed during life by the finding of cystine crystals in a smear of the sternal marrow.

In 1936 Fanconi published his important paper on a type of osteodystrophy associated with renal glycosuria, aminoaciduria and hypophosphataemia. These findings were interpreted as being evidence of a renal tubular dysfunction. He described three cases of this syndrome, the first of which was a girl who died at the age of 5½ years with rickets and dwarfism. At necropsy it was noted that the cells of the renal tubules had the appearance of having been packed with a substance which had been dissolved out during the process of fixation either by water or alcohol. Sturzenegger (1939) has suggested that this substance might well have been cystine. Fanconi's third case was a girl of 2½ years who presented with rickets and malnutrition and was found to pass both sugar and organic acids in the urine. This child was kept under observation until her death (in 1939) at the age of 8 years from renal failure with an enlarged liver and spleen (Fanconi, 1946). Post-mortem examination revealed extensive cystinosis throughout the body. In his 1946 paper Fanconi described another case of cystinosis occurring in a girl aged 1 year in whom the diagnosis was made during life by marrow examination and confirmed by necropsy. In his most recent paper on the subject (Fanconi and Bickel, 1949) he reported the case of a 14-month-old girl exhibiting the clinical features of the 'Fanconi syndrome' whose marrow had been found to contain cystine crystals. Very similar to this case is the little boy described by d'Avignon and Vahlquist (1949) who again showed the clinical features of the Fanconi syndrome. The authors failed to demonstrate cystine crystals in the marrow but based their diagnosis on the observation of crystalline deposits in the cornea and conjunctiva exactly resembling those described by Bürki in Hottinger's case. Hottinger (1947) has also

reported a second case of cystinosis. The patient, a boy of 1 year, presented with severe hypophosphataemic rickets and died suddenly from an apparently slight respiratory infection. An older child, who is still alive in spite of progressive renal failure, has been described by Ullrich (1948) who made the diagnosis of cystinosis on the finding of crystalline deposits in the conjunctiva, cornea and iris. A remarkable feature of this case is the family history. The patient is the sole survivor of eight siblings, six of whom have died of symptoms suggestive of cystinosis.

Freudenberg (1949) quotes Schmidt who states that one of the two children reported by Pache (1940) had died at the age of 7¾ years and that cystinosis was found after death. These two children, who were brother and sister, both showed marked rickets and dwarfism associated with cystinuria, but cystinosis was not demonstrated during life. The other child, the sister, has also died but no record of necropsy is available.

Finally Roulet (1941) has argued that a case described by Benoit (1938) as calcinosis universalis was probably one of cystinosis. The child, a boy of 3¾ years, suffered from severe malnutrition and rickets. At necropsy the tissues were found to contain large numbers of translucent, polygonal crystals which Benoit considered to be calcium but which Roulet has shown might well have been cystine.

In addition to the 16 cases mentioned above in which rickets and dwarfism were shown to be associated with cystine deposition in the tissues, two further cases have been reported in which cystinosis was discovered after death without there being any definite preceding history of rickets. The first of these was a boy who died at the age of 21 months of inanition and was reported by Abderhalden (1903). Kaufmann (1929), who did the necropsy on this case, described the deposition of cystine crystals in the body tissues. Rössle's (1938) case died of renal failure, and extensive deposits of a substance believed to be cystine were found throughout the body.

Table 2 lists five cases of cystinuria in children where a diagnosis of cystinosis has been suggested but not proved. Three of these cases had clinical hypophosphataemic rickets while a fourth died of renal failure.

Case Report

Jacqueline R., aged 7½ years, was admitted to The Hospital for Sick Children, on August 20, 1948. The history indicated that she had been an apparently normal child until the age of 3 years. Pregnancy and labour had been normal; her birth weight was 8 lb. 10 oz. She was breast fed for the first six months when mixed feeding was begun. The usual vitamin supplements were added to the diet from the age of 1 year. She was a little late in passing the developmental milestones, standing at 11 months and walking at 17 months. She cut her first tooth at 1 year and had a complete set at 2. She had measles at the age of 3 years.

At the age of 3½ years she was taken to another hospital on account of irritability, anorexia and apathy. No bony abnormalities were noted and no radiographs were taken but a diagnosis of rickets was made and she was given vitamin D tablets and ultra-violet light. There was a steady improvement in her condition and she was discharged after attending for 15 months.

When she was 5 years old she started school and was found by the medical officer there to be undersized. She was admitted to a second hospital for investigation. There the dwarfism was confirmed, the weight being only 25 lb. The intelligence seemed normal. There was epiphyseal thickening and she stood with the knees in the valgus position. The eyes appeared normal except that ' very early choroidal atrophy at the periphery of the retina ' was noted. The blood pressure was 100/65. The liver and spleen were not palpable. The urine had a specific gravity which varied between 1010 and 1020, and contained small amounts of albumin. No glycosuria was discovered in five examinations. Investigation of the blood chemistry gave the following results: blood calcium, 7·6 mg. per 100 ml. of serum; blood phosphorus, 7·5 mg. per 100 ml. of plasma; blood urea, 175 mg. The alkali reserve was 28·7 vols. of CO_2 per 100 ml. of serum. The serum protein level was 7·8 g.% (albumin 5·0 g., globulin 2·0 g.).

A diagnosis of renal rickets was made and she was discharged. She remained fairly well during the following year except that the knock-knee deformity increased considerably.

One year before admission, when she was 6 years old, she had what appears to have been her first attack of typical carpo-pedal spasms. She had three further attacks during the subsequent six months. Twice weekly calcium gluconate injections and large doses of radiostoleum were given. The appetite had been poor for some time. Thirst was stated to be excessive since infancy but less so during the last six months. Five days before admission she developed a sudden attack of diarrhoea with occasional vomiting and on the preceding day she became drowsy and developed rapid, deep respiration.

Both parents are healthy. Jacqueline was the first of three children. The second died of ' stoppage of the bowel ' at the age of 9 months, and the third, a girl of 3 months, is well. There was a stillbirth two years before.

Examination showed her to be a normally intelligent but drowsy little girl with considerable dwarfing and deformity (height 34½ in., weight 24 lb. 12 oz.). She was apyrexial and had deep and rather rapid respirations. The skin was dry and coarse and of an earthy pallor. There were a few scattered ecchymoses. The hair was very fine. She suffered from considerable photophobia and kept her eyes screwed up in all but the dimmest

TABLE

RECORDED CASES

Case	Author	Sex	Age at Onset	Family History	Rickets	Dwarfism	Eye Changes	Liver	Spleen	B.P.	Blood		
											Alkali Reserve (Vol. of CO_2 %)	N.P.N. (mg. %)	Ca. (mg. %)
1	Lignac (1924a)	M.	1 yr.	–	++++	+	–	o	o	–	–	–	–
2	Lignac (1924b)	M.	18 mo.	?+	++++	–	–	–	–	–	–		–
3	Lignac (1924c)	F.	?	–	+	–	–	–	–	–	–	–	–
4	Benoit (1935) Roulet (1941)	M.	?	–	++++	++	–	–	–	–	–	–	–
5	Russell and Barrie (1936a)	F.	14 mo.	?+	++++	++	o	–	o	+	–	(34)	9·7
6	Russell and Barrie (1936b)	M.	18 mo.	o	++	?	o	o	+	+	–	–	–
7	Fanconi (1936) Sturzenegger (1939)	F.	3 mo.	o	++++	++	–	o	o	–	–	40 83	–
8	Beumer and Wepler (1937)	M.	9 mo.	o	++++	+	o	o	o	–	–	26 98	–
9	Pache (1940b)	M.	8 mo.	+	++++	++	o	–	–	+	–	23	10·8
10	Hottinger (1941)	M.	1 yr.	+	++++	++	Conjunctival and corneal deposits	+	+	–	–	29 129	11·5 5·1
11	Fanconi (1946a)	F.	1 yr.	+	+++	+	o	+	o	80/40	32	39 214	9·87
12	Fanconi (1946c)	F.	Birth	?	+++	+	o	o	o	120/70	46	39 93	10·2
13	Hottinger (1947)	M.	10 mo.	o	++++	o	o	+	+	–	–	–	7·5
14	d'Avignon and Vahlquist (1949)	M.	9 mo.	o	++++	++	Conjunctival and corneal deposits	o	o	–	12·25	32	12·4
15	Fanconi and Bickel (1949b)	F.	14 mo.	+	+	++	o	+	o	105/65	34	21	9·0 11·0
16	Ullrich (1948)	M.	1 yr.	++	+++	++	Photophobia. ? Deposits in conjunctiva, iris and cornea	+	–	120/65	–	78 135	6·7 4·6
17	Abderhalden (1903) Kaufmann (1929)	M.	–	+	–	–	–	–	–	–	–	–	–
18	Rössle (1938)	F.	2 yr.	–	–	+	–	o	o	–	–	–	–

Where more than one value is reported the figures given represent the extremes.

TABLE

RECORDED CASES OF CYSTINURIA WITH

Case	Author	Sex	Age at Onset	History	Rickets	Dwarfism	Eye Changes	Liver	Spleen	B.P.	Blood		
											Alkali Reserve (Vol. of CO_2 %)	N.P.N. (mg. %)	Ca. (mg. %)
1	Russell and Barrie (1936c)	M.	4 yr.	–	o	o	Photophobia. Retinitis	o	o	240/170	–	(126)	
2	van der Zijl and Heslinga (1940)	M.	–	o	–	+	o	o	o	–	–	–	10·2
3	Pache (1940a)	F.	8 mo.	+	++	+	o	–	–	90/70	–	30	9·4 11·8
4	Lelong (1938) Fanconi (1936)	F.	4 mo.	o	+	+	o	+	o	70/?	35	55	8·0 9·5
5	Van Creveld and Grunbaum (1941)	M.	14 mo.	+	++	+	o	+	+	–	34	28	10·8

Where more than one value is reported the figures given represent the extremes.

TABLE 1
OF CYSTINOSIS

Blood		Urine							
P. (mg.%)	Phosphatase (units)	Reaction	Alb.	Sugar	Amino-acids	Cystine	Outcome	Age at Death	Evidence of Cystinosis
–	–	Acid	+	+	–	–	Died of acidosis and vomiting	3 yr.	At necropsy
–	–	–	+	o	–	–	Died of urinary infection	2 yr.	At necropsy
–	–	–	–	–	–	–	Died Hydrocephalus	14 mo.	At necropsy cystinosis, cystine calculi
–	–	–	–	–	–	–	Died of tetany	3½ yr.	At necropsy ? cystinosis
2·7	–	–	+	+	–	–	Died of uraemia and hypertension	12 yr.	At necropsy
–	–	–	++	o	–	–	Died. ? Uraemia and hypertension	16 yr.	At necropsy
–	–	–	++	++	–	–	Died	5½ yr.	At necropsy ? cystinosis
–	–	–	++	++	–	–	Died of uraemia and marasmus	–	At necropsy
3·9	–	Acid	+	o	–	+	Died of uraemia	7¾ yr.	At necropsy
7·2 9·4	–	–	++	+	+	o	Died of uraemia and tetany	7¼ yr.	Cystine deposits in sternal marrow. At necropsy cystinosis
2·3 12·3	18	Neutral	+	o	+	100 mg. daily.	Died of renal failure	8 yr.	At necropsy
3·0	7	Alkaline	+	o	–	+	Died of gastro-enteritis and pneumonia	3¾ yr.	Cystine deposits in sternal marrow. At necropsy cystinosis
2·38	–	Neutral	+	o	–	–	Died of slight respiratory infection	1 yr.	At necropsy
3·6 4·2	12	Neutral alkaline	+	+	+	o	Improving Treated vitamins A, D and citrates	–	Diagnosis on eye signs. Sternal marrow negative
2·0	5	Neutral acid	+	+	+	o	Alive	–	Cystine deposits in sternal marrow
4·9	–	Acid	++	o	–	–	Alive aged 12 years. Renal failure	–	Diagnosis on eye signs
–	–	–	–	–	–	–	Died of inanition	1¾ yr.	At necropsy.
–	–	–	–	o	–	–	Died in coma	4 yr.	At necropsy diffuse crystalline deposits, probably cystine

( )=Figure expressed as blood urea. +=Positive finding. o=Negative finding. –=Finding not recorded.

TABLE 2
SUGGESTED DIAGNOSIS OF CYSTINOSIS

Blood		Urine							
P. (mg.%)	Phosphatase (units)	Reaction	Alb.	Sugar	Amino-acids	Cystine	Outcome	Age at Death	Evidence of Cystinosis
–	–	–	++	–	–	+	Died of uraemia	13 yr.	Cystine calculus removed at 4 years. Biopsy, early nephritis. Necropsy, chronic nephritis, no cystinosis
6·3	–	–	+	o	+	+	Alive aged 12		
2·97 4·1	–	Acid alkaline	+	o		9 mg. daily.	Died	8 yr.	No record of necropsy
3·75	7·7	–	++	+	+	+	Died. Pyrexia and constipation	5¾ yr.	No necropsy
1·9 2·8	12 34	Neutral alkaline	+	o	+	+	Alive aged 5		

( )=Figure expressed as blood urea. +=Positive finding. o=Negative finding. –=Finding not recorded.

lights. There was some thickening of the palpebral margins. The corneae were noticed to be clouded and the retinae showed a diffuse black and white reticulation. A more careful examination was made by Mr. J. H. Doggart who reported:

'Both corneae show innumerable punctate opacities in the superficial layers. There is no breach of the surface. Both fundi show widespread choroido-retinal degeneration with partial consecutive optic atrophy.' The tongue was moist with a little brown fur posteriorly. There was gross dental caries. The throat was clean and the tonsils appeared healthy. The lungs seemed normal except for some fine crepitations at the right base. The heart was slightly enlarged but the sounds were normal. The blood pressure was 155/90. The liver and spleen were both enlarged to about three finger-breadths below the costal margins and were firm and smooth but not tender. No enlarged lymph nodes were palpable. Examination of the skeletal system showed slight frontal bossing of the skull which had a circumference of 19¾ in. Some bossing was noted at the costochondral junctions. The spine was normal. Valgus deformity was present at both elbows. The lower ends of the radius and ulna were thickened and there was some ulnar deviation at the wrists. The knees and to a lesser extent the ankles showed valgus deformity.

FIG. 1.—Radiograph showing both knees and ankle joints. Note thin cortex and osteoporosis, also enlarged and woolly metaphyses with cupping at the distal end of the tibia.

Pathological investigations showed: haemoglobin 38% (Sahli) 5·2 g. per 100 ml.; red blood cells 1·82 million per c.mm.; leucocytes 12,300 per c.mm. (polymorphs 64%, lymphocytes 33%, eosinophils 3%); platelets 220,000 per c.mm. The blood Wassermann and Kahn reactions were negative.

Blood analysis gave: urea, 229 mg. per 100 ml. blood; protein, 6·3 g. per 100 ml. plasma; calcium, 4·9 mg. per 100 ml. serum; phosphorus, 8·4 mg. per 100 ml. serum; potassium, 11·2 mg. per 100 ml. serum; chloride, 628 mg. per 100 ml. serum; bicarbonate, 27 vols. CO_2 per 100 ml. plasma. The alkaline phosphatase was 29·6 King-Armstrong units.

The urine was acid, with a specific gravity of 1009. An Addis count gave: protein, 500 mg.% per 24 hours; red cells, 7,265,000; leucocytes, 21,311,000; casts, 84,000.

Analysis for the presence of cystine showed 1·1 mg. per 100 ml. The urinary output varied from 14 to 26 oz. per day but accurate measurement was only occasionally possible owing to incontinence.

FIG. 2.—Radiograph of left forearm showing similar changes.

An x-ray report (Dr. L. G. Blair) stated: 'Marked and extensive rachitic changes in the long bones (Figs. 1 and 2). No abnormality in the skull. The heart is enlarged; lung fields congested: bilateral minimal pleural effusions.'

In view of these findings a diagnosis of renal rickets with uraemia was made though the possibility of cystinosis was later considered. The child was treated with 30 ml. of a mixture containing sodium citrate 100 g., citric acid 60 g., water 1,000 ml., in four-hourly doses. She also received large doses of calcium lactate and vitamin D. A small blood transfusion was also given. In spite of these measures the child's condition steadily deteriorated. She developed heart failure with oedema, ascites, and bilateral pleural effusions, and increasing uraemia. She died on September 17, 1948.

A post-mortem examination by Dr. Martin Bodian showed that the body was that of a stunted and wasted child with moderate oedema.

There was slight frontal bossing of the skull. Whitish deposits were found on the pia arachnoid membrane, especially along the sagittal edge of the occipital and parietal lobes. The brain was normal. The tonsils were enlarged, and on section showed a greyish-white finely reticular pattern.

There were bilateral small pleural effusions. The fluid contained hexagonal and rod-shaped crystals. In the lungs were pinpoint subpleural deposits of shimmering white material, some pulmonary oedema and lobular consolidation. There was some pericardial effusion. The fluid resembled that found in the pleural cavities. The visceral pericardium appeared frosted. There was some hypertrophy and dilatation of the left ventricle. There was a small amount of ascites in the abdomen, and the fluid again contained crystals. Numerous chalky patches were seen on the parietal peritoneum and greater omentum.

The liver was enlarged, pale and smooth. Beneath the serosa there was a punctate, fern-like pattern of silvery-white deposits uniformly distributed throughout the whole surface. These were less noticeable on cut section.

The gall-bladder and pancreas were normal. The spleen was enlarged and salmon pink.

There were two or three circular white plaques on the surface. On section the normal markings were replaced by a finely linear and punctate silvery-white pattern interspersed with pale brown areas on a salmon pink background.

The suprarenals were normal.

The kidneys were very small and firm with numerous small cortical cysts. On section the normal pattern was completely lost. The cortex was very thin and there were radially directed linear markings of pale cream colour in the medulla.

There were small white specks on the mucous membrane of the stomach and small intestine.

The reproductive organs were normal.

Four parathyroid glands were discovered and considered normal in size and shape.

Lymph nodes were enlarged and pale, containing opaque white deposits.

There was broadening and heaping up of the epiphyseal plates. The red bone marrow contained bright yellowish streaks and flecks of chalky material. The sternum contained only four small islands of marrow.

Histology. There was a widespread deposition of double refractile crystals within the cells of the reticulo-endothelial system. There was no foreign body giant cell reaction to the presence of these crystals, which were found in the choroid, iris and cornea of both eyes, in the duodenum and caecum within phagocytes, in the liver in Kupffer cells and within phagocytes in the portal areas, in the medullae of the adrenals, in the spleen and in numerous lymph nodes, in the medullae of both kidneys, in the urinary bladder and in one section of femur. These crystals were identified as cystine by x-ray crystallographic analysis. There was extensive destruction of the nephrons as well as marked changes in the renal vessels attributable to gross renal destruction. Changes observed in the bones were consistent with renal rickets.

Discussion

The diagnosis of cystinosis depends on the demonstration of cystine crystals in the tissues. In 13 of the recorded cases this was shown at necropsy, the diagnosis not having been suspected during life. In these cases cystine crystals were found throughout the body, notably in the organs of the reticulo-endothelial system and in the kidneys. In only five reported cases has the diagnosis been made during life. In Hottinger's (1941) first case the corneae were hazy due to the presence of large numbers of minute refractile crystals in the cornea and conjunctiva. Histological examination at a later date showed these crystals to be cystine (Bürki, 1941). Ullrich (1948) and d'Avignon and Vahlquist (1949) have used similar clinical observations in their cases to substantiate the diagnosis of cystinosis. In our patient an almost identical appearance was seen in the cornea but conjunctival deposits were not observed. The retinal changes have not been previously described. Russell and Barrie (1936) mention retinitis in their third case but this was probably albuminuric in type.

An interesting symptom observed in our case was marked photophobia. This symptom is emphasized by Ullrich and the photograph of Hottinger's first patient (Bürki) would suggest a similar occurrence. It is conceivable that the presence of refractile crystals in the cornea might increase the dazzle effect produced by bright lights. Bürki recommends the use of a slit lamp as an aid to diagnosis in all cases of renal osteodystrophy.

A somewhat easier means of establishing the diagnosis of cystinosis during life seems to be the examination of smears of bone marrow. In cystinosis large reticulum cells containing refractile cystine crystals may be observed. This finding was first described by Esser (1941) in Hottinger's first case and observed again by Fanconi (1946) in his third case and by Fanconi and Bickel (1949). d'Avignon and Vahlquist, however, were unable to demonstrate cystine crystals in the small amount of marrow aspirated from the tibia in their case and we were unable to obtain any marrow from the sternum in ours. At necropsy it was seen that the sternal marrow had become confined to four small islands. It is unfortunate that the procedure of iliac crest puncture was not being practised at that time. The diagnosis of cystinosis might also be established by means of biopsy of some suitable tissue, for instance a lymph node. In Russell and Barrie's third case a biopsy was taken from the renal cortex at the time of operation for removal of a cystine calculus but no evidence of cystinosis was demonstrated. In this connexion it is important to remember that cystine is soluble in the ordinary fixatives such as formalin, used in the preparation of histological sections (Roulet, 1941). All biopsy and post-mortem material should be fixed in alcohol only. In our case the examination of the fluid which had collected in the various serous cavities would presumably have confirmed the diagnosis.

The finding of increased amounts of cystine in the urine does not in itself justify the diagnosis of cystinosis. Cystinuria has been demonstrated in only four of the described cases. In our case the single estimation gave a value only slightly in excess of normal. On the other hand several of the cases of cystinosis have a family history of cystinuria. Lewis (1932) examined 10,500 healthy students and found cystine crystals in the urines of four, while a further 14 gave a strongly positive reaction to tests for cystine. According to Linder (1944)

approximately 10% of cystinurics develop cystine calculi in the renal tract. Table 2 gives details of five cases from the literature in which cystinuria has been found to be associated with either rickets or dwarfism and a diagnosis of cystinosis has been suggested. Three of these have died. In two of them necropsy was either not performed or not reported, while the third showed no evidence of cystinosis. The fate of the other two has not been reported and without further evidence it seems wrong to include any of these as cases of cystinosis. Of a milder nature are the two cystinuric sisters reported by Hickmans and Smallwood (1935) who had associated albuminuria, and, though not dwarfed, are described as being slender and delicate.

The clinical picture of cystinosis may perhaps be divided into three stages. These stages are not sharply delimited and usually overlap one another considerably. Up to the age of about 2 years the child fails to thrive. There may be a tendency to excessive reaction to infection or intoxication with undue thermolability, dehydration and constipation. Examination will show an underweight infant whose urine is alkaline and contains albumin and perhaps a little sugar. In spite of the urinary reaction the alkali reserve of the blood is much reduced. The condition thus somewhat resembles the syndrome of nephrocalcinosis described by Lightwood (1935). It appears that confusion between these two conditions may also occur at necropsy. Roulet has shown that Benoit's (1935) case of calcinosis universalis was in all probability one of cystinosis. Both calcium and cystine give a positive von Kossa reaction.

The second and perhaps most important stage is clinically indistinguishable from the syndrome described by Fanconi (1931), De Toni (1933), and Debré, Marie, Cléret and Messimy (1934) and called by the first author amino-diabetes. McCune, Mason and Clarke (1943) give a detailed analysis of cases of this syndrome reported before 1943, and of the 40 cases included seven had cystinosis. The characteristic features of this stage are rickets and dwarfism associated with excessive thirst, polyuria and certain biochemical disturbances. The urine, which is usually alkaline, has a low specific gravity and contains a small to moderate amount of albumin, large quantities of phosphates, amino-acids and occasionally sugar. The study of the various amino-acids excreted has been aided recently by the introduction of partition chromatography. Examination of the blood shows a normal calcium level but reduced phosphorus. The level of the alkaline serum phosphatase may be slightly raised. The blood urea is normal. The fasting blood sugar is normal but there may be a diabetic type of response to the administration of glucose. Radiologically the changes differ from those seen in ordinary vitamin D deficiency rickets. There is rarefaction of the bone structure and widening of the epiphyseal line without any proliferation of osteoid tissue. Nor is there any increase in the distance between the epiphysis and the metaphysis. According to Fanconi (1946) these findings resemble those seen in Gaucher's disease and certain chronic anaemias.

The final stage is one of renal failure with uraemia and hypertension. The level of the serum phosphorus rises while that of the calcium falls so that several of the children have suffered from tetany. At this stage there may be some enlargement of the liver and spleen. The clinical picture now resembles that of classical renal rickets as described by Barber (1921) and others, with the addition perhaps of hepatosplenomegaly and the appearances of cystine deposition in the eyes.

No treatment so far suggested appears to have had any markedly beneficial effect. It seems to be wise to avoid cystine- and cystein-rich foods. Alkalies in the form of Albright's (Shohl's) mixture might help to reduce the acidosis. Large doses of vitamin D should be used to combat any superimposed deficiency rickets which is said to occur.

The prognosis is hopeless. If the child survives the first stage of thermolability he will succumb later to renal failure.

Aetiology and Pathogenesis. It is not proposed to discuss the pathogenesis and biochemical relationships of cystinosis in any detail. Our own case was unfortunately under observation for too short a time to permit relevant study.

It is evident that the condition has a genetic basis. Many of the recorded cases have a family history of either cystinosis, cystinuria or consanguinity. It is perhaps significant that eight of the cases come from Switzerland where intermarriage is relatively common.

According to Fanconi (1946) the disease is primarily one of disordered protein metabolism, there being abnormal amino-acid production following the breakdown of albumin. He postulates that the resulting albumin deficiency gives rise to retarded growth and to the characteristic osteodystrophy. The amino-acids produced are excreted by the kidneys and may be found in the urine but are at the same time nephrotoxic. Experiments by Curtis and Newburgh (1927) and others have shown that young animals fed on a diet containing large amounts of cystine develop renal lesions resembling glomerulo-nephritis. The renal damage is progressive and eventually the patient

will succumb to uraemia with contracted kidneys. As in all cases of chronic renal failure in childhood classical hyperphosphataemic rickets develops. The renal failure also tends to hold back the excretion of cystine which is already being produced in excess, with the result that it is deposited throughout the tissues especially in the reticulo-endothelial system. Freudenberg (1949) has argued that this blocking of the reticulo-endothelial system is responsible for the very poor response which these children show to ' intoxication ' and infection.

An entirely different conception of the disorder is held by Debré (1946) who believes that the primary pathology is in the renal tubules.

Summary and Conclusions

The literature relating to cystinosis (cystine storage disease or Lignac's disease) is reviewed.

A case of cystinosis in a girl dying of uraemia at the age of 7½ years is described. The diagnosis had been suggested during life by the finding of crystalline deposits in the corneae. Changes in the retinae are also described. A description of the clinical features of the condition is given and the aetiology briefly discussed. The treatment of the disorder is of little value and the prognosis hopeless. It is felt that although cystinosis is undoubtedly very uncommon, cases are probably overlooked because the condition is not borne in mind.

I wish to thank Dr. W. G. Wyllie under whose care this case was treated for his encouragement and permission to publish, Dr. L. G. Blair for allowing me to reproduce his radiographs and Dr. C. E. Dent for the chemical analysis of the crystals.

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CHRONIC PANCREATITIS IN CHILDHOOD

BY

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Chronic pancreatitis in childhood is a disease which has very rarely appeared in the literature; indeed Davis and Kelsey (1951) in their recent review of the literature were able to find only three cases, to which they added one of their own, so making a total of four recorded cases.

When this condition is mentioned in paediatric textbooks it makes only the briefest appearance which gives little or no idea of the variations of symptomatology of which the illness is capable, nor of the magnitude of the diagnostic problem which may indeed be left unsolved. It is probably this latter difficulty which is the reason for so few case reports. The case reported is the youngest to be recorded.

Case Report

A.J.A. (No. 26154), a boy, aged 3 years, was admitted to the Duchess of York Hospital for Babies, Manchester, with the chief complaint of a swollen abdomen for at least two weeks. The mother was the informant, but she gave a strong impression that she was not a reliable witness and it was not unreasonable to believe that the onset of the illness dated back more than two weeks. She had noticed wasting of the patient 10 days before admission, the face, arms and chest becoming strikingly thin. The child had complained of abdominal pain, and he had vomited once nightly for three nights before admission. Also alternate loose and normal bowel evacuations were noted, but no blood in the stools. There had been no change in the patient's appetite which remained good up to the time of admission.

Pregnancy had been normal throughout and gestation brought to term. Labour and delivery were normal and neonatal progress uneventful. The birth weight was over 6 lb. (2·7 kg.). The first teeth erupted at 8 months, at which age also the baby sat alone for the first time. At 16 months he was able to walk alone, and at 2 years was able to utter intelligible words. He had been immunized against diphtheria and pertussis, and the only illness contracted had been measles. There was no history of accident or abdominal trauma.

The father was well and 28 years old, the mother 27 years of age and well, although she did state that for many years since childhood she had 'been troubled with her chest' and there was some question about a haemoptysis at 14 years of age, but she had been radiographed five years previously, the lungs being reported clear. There were three siblings, a boy aged 5 years and well, a girl aged 4 years and well, and another boy aged 2 years and well. The mother had had one miscarriage, of unknown cause. No familial disease or trait was admitted.

Home conditions were very bad with strong evidence of neglect by the parents, but the other children of the family appeared well nourished. It is, perhaps, appropriate to mention here that throughout the patient's stay in hospital not once did either parent visit him, despite importuning on the part of the hospital staff, and it was only after the child had been recovered for some time that the mother could be persuaded to fetch him home.

Physical examination on admission showed a pale, wasted, chronically ill, red-haired boy. His temperature was 100·2° F. (38° C.), pulse 146, respiration 28 per minute. His weight was 23 lb. 9 oz. (10·7 kg.). The head circumference was 17 in. (43 cm.) and height 31 in. (79 cm.). In striking contrast to the wasted face, chest and extremities was a grossly distended abdomen, tense to palpation and dull to percussion, from which was also elicited a fluid thrill. No masses could be palpated, there was no noticeable tenderness, and no prominence of the superficial veins. There was a fair degree of pitting oedema about the sacrum and lower lumbar region and on the legs, ankles and dorsum of the feet, but nowhere else.

The other abnormal findings were a cardiac systolic murmur, most audible in the mitral region, and some diminished air entry into both lung bases. The immediate impression was that the patient was suffering from chronic tuberculous peritonitis.

A Mantoux test (1 : 10,000 dilution of old tuberculin) was negative after 48 hours as were consequent 1 : 1,000, 1 : 100 and 1 : 10 dilutions. On the day after admission an abdominal paracentesis was carried out and 20 oz. (560 ml.) of a light, reddish fluid removed. This ascitic fluid was obviously bloodstained and it contained, besides many red and white blood cells, some lumps of coagulum. There was little reduction of the distended abdomen following the paracentesis.

By the ninth hospital day the oedema over the lower back region was no longer present, but a mass suspected of being an enlarged spleen was palpated in the left hypochondrium, a fingerbreadth below the costal

margin. The ascites increased and a second paracentesis was done on the eleventh hospital day, with the removal of about 11 oz. (310 ml.) of a clear, straw-coloured fluid. The patient's general condition continued much the same as on admission.

An intravenous pyelogram showed a normal excretion of dye by both kidneys and no abnormality of the renal structures.

By the fifteenth hospital day, although there were signs of clinical improvement in the patient's general condition, the firm, smooth liver edge became palpable two fingerbreadths below the costal margin in the mid-clavicular line and this edge extended across the epigastrium and seemed to merge with the splenic mass. The abdomen by this time had become soft; without further paracenteses it no longer had any trace of ascites and all signs of the pitting oedema previously noted had disappeared. No therapeutic measures had been introduced.

By the nineteenth day the mass taken to be the spleen reached the level of the iliac crest, but three days later both this mass and the liver appeared to be receding. There was no associated lymphadenopathy and there was a progressive fall in the leucocyte count with a rise in the lymphocytes.

The child's general condition continued to improve, and on the twenty-fifth hospital day a tibial marrow puncture was done, but gave no lead to the diagnosis. Except for an intermittent spiking of the temperature the child appeared well, was of good colour, jolly and active by the twenty-ninth day. The abdomen was soft and small, but the receding splenic mass was still just detectable beneath the left costal margin. This mass and the liver edge were still palpable by the forty-first hospital day. On the forty-seventh hospital day the patient complained of some abdominal pain about the umbilicus where he was somewhat tender, and, although still lively, he spiked a febrile temperature and an indistinct mass was felt deep in the left hypochondrium and umbilical region. The spleen tip was only just palpable and the liver edge was one fingerbreadth down. The possibility of the deep mass being the pancreas was considered. A few days later, however, the abdomen was negative to examination and the child appeared very well in himself. He was active, playful, even mischievous about the ward. His body had filled normally and his general appearance was that of a chubby, healthy child. His weight during his stay in hospital changed from 23 lb. 9 oz. (10·7 kg.) on admission, to 22 lb. 15 oz. (10·4 kg.) by the twenty-fifth hospital day, to 26 lb. 12 oz. (12·1 kg.) by the fifty-first, and on the day of discharge, 85 days after admission, it was 27 lb. (12·3 kg.), or 3 lb. 7 oz. (2·5 kg.) more than on admission.

Laboratory Data. On May 29, 1951, ascitic fluid was withdrawn. It was brownish-red, turbid, with a mass of coagulum, and alkaline to litmus, with a specific gravity of 1010. Urea was 0·2 g. %. There was a deposit consisting of many pus cells and red blood cells. Protein was 3 g. %. No bacteria were seen on Gram staining.

On June 7 no malignant cells were detected on microscopy of the ascitic fluid, but a heavy deposit of leucocytes, lymphocytes predominating, was seen. The erythrocyte sedimentation rate was 3 mm. in one hour. Haemoglobin was 70%; erythrocytes 4·0 m.; white blood cells 14,400 (polymorphs 70%, lymphocytes 20%, eosinophils 6%, monocytes 4%). On May 31 platelets were 480,000 per c.mm., and on July 26 haemoglobin was 76%, erythrocytes 3·9 m., white blood cells 8,500 (polymorphs 45%, lymphocytes 48%, eosinophils 6%, basophils 1%).

On May 29, 1951, blood urea was 25 mg.%, and on May 30 examination of the urine gave an acid reaction, with a trace of protein, no sugar or acetone and nothing abnormal in the deposit. On July 10 the urine was normal.

Faeces were examined on June 28 and again on July 3 and 9, but no salmonella or dysentery organisms were isolated.

Between June 7 and July 16 faeces, gastric washings and ascitic fluid were examined, but no tubercle bacilli were isolated.

On July 5 serum amylase was 800 units % (normal values 90-163). On July 9 the urinary diastase index was 80 Wohlgemuth units (normal 6-30), on July 25 it was 5 W.u., and on July 27 10 W.u. On August 14 serum amylase was 133 units % and the urinary diastase index 20 W.u.

A mumps neutralization test on August 16 was negative.

Wassermann and Kahn reactions were negative. Radiographs showed a benign bone cyst in the proximal metaphysis of the right humerus.

Discussion

In this case report of chronic pancreatitis in a boy of 3 years the diagnosis was reached by a process of exclusion, biochemical evidence of the disease still being present 54 days after the probable onset of the illness. Elman (1931) states that ' blood from patients with a normal pancreas has a normal blood amylase, whereas deviations from the normal are found only in cases of proved disease of the gland '. In the acute forms of pancreatitis the serum amylase level rises sharply within a few hours and falls to normal again in 24 to 48 hours (Wightman, 1948). In the chronic form without acute exacerbations and in the quiescent intervals of the chronic relapsing type the serum amylase is usually normal (Cantarow and Trumper, 1949). The serum amylase and lipase were elevated in the case of chronic relapsing pancreatitis in a boy of 8 years who was observed by Collett and Kennedy (1948) in an acute phase. The raised blood amylase in the case of Davis and Kelsey (1951) and in the present case is therefore of added interest. In the case of Davis and Kelsey the blood amylase determinations were made after the diagnosis had been established by operation and biopsy, and the amylase levels remained high for over 12 months, a most

unexpected sequel. In the present case the high serum amylase, assayed by King's (1951) modification of Wohlgemuth's (1910) method, and the urinary diastase index fell to normal fairly quickly. An estimation of the amylase in the ascitic fluid would have been of great interest.

There is as yet no definitive clinical picture of chronic pancreatitis in childhood, but from the very few recorded cases in children it is suggested that the cases fall into two broad groups, chronic relapsing pancreatitis as discussed in a symposium by Gambill (1947), Baggenstoss (1947), and Comfort (1947) and chronic interstitial pancreatitis without the acute exacerbations which Opie (1910) described.

Abdominal pain is common. Collett and Kennedy's (1948) case, a boy of 8 years, had had recurrent attacks for four years. These had been severe on six occasions and five times had resulted in surgical exploration. Pains occurred in the two cases of Gambill (1947), and that of Davis and Kelsey, and in the present case they appear to have been very mild indeed. Opie in his account of chronic pancreatitis in adults lays no stress at all on abdominal pain.

Ascites has been less common, but was prominent in Davis and Kelsey's case and in my case, in which there was great abdominal distension. The appearance of the ascitic fluid in both cases was very similar. The first paracentesis in each case produced a reddish fluid which in my case had become amber 10 days later. In Davis and Kelsey's case repeated paracentesis produced a reddish fluid which became amber-coloured at operation nine days later. Vomiting was conspicuous in the others, but only slight in my case. Food precipitated the pain in one of the two cases of Comfort, Gambill and Baggenstoss (1946). Weight loss with wasting and oedema has not been uncommon, having been remarked upon in three of the five cases. Hepatomegaly was present in one of the cases of Comfort *et al.*, and there was also splenomegaly in the case of Collett and Kennedy (1948) and in my case. Collett and Kennedy's case showed abnormal liver function tests.

The very striking enlargement of the spleen in the present case and its eventual complete recession is not easily explicable. A hypothesis is that the pancreas became swollen by whatever pathology was affecting the gland and that the swelling compressed and occluded the splenic vein, producing back pressure and passive congestion of the spleen which resolved *pari passu* with the recovery of the pancreas. Some weight is lent to this hypothesis by Opie (1910) who remarks upon the likelihood of the splenic vein becoming thrombosed in the acute haemorrhagic forms of pancreatic disease. By inference it is a possibility that thrombosis of the splenic vein was the cause of the splenomegaly whose resolution was brought about by re-canalization and/or the opening up of subsidiary channels. And Comfort *et al.* (1946) say 'splenomegaly (chronic passive congestion) may well be due to partial obstruction of the splenic vein'.

One of the cases of Comfort *et al.*, complicated by diabetes mellitus, developed oedema of the face, legs and lower part of the back, and ascites. Davis and Kelsey's patient had minimal pitting oedema of the legs with ascites, and my case had marked pitting oedema of the lower extremities and the lower back associated with marked ascites.

The case of Collett and Kennedy (1948) was remarkable in that it was associated with hyperlipaemia. Xanthomatous lesions of the skin were present from 15 months to 2 years of age and then disappeared on a low-fat diet. This is the only case in childhood with this manifestation, although Thannhauser is quoted as citing cases of hyperlipaemia with secondary xanthomatosis associated with chronic pancreatitis in adults.

Comfort (1947) pointed out the frequency of deposits of calcium in the pancreas, which were shown by radiography in 13 of 29 adult cases, but such deposits have not been demonstrated in children. Polymorphonuclear leucocytosis of moderate degree with eosinophilia and a raised erythrocyte sedimentation rate may be present.

There is no clear understanding of the cause of the disease as it occurs in early childhood. In his series of adult cases Opie gives as aetiological factors obstruction to the outflow of the gland's secretion by the pancreatic ducts (in 10 of 30 cases, pancreatic calculus in the duct of Wirsung); biliary calculi in the adjacent terminal part of the bile duct; new growths; ascending infection from the duodenum; arteriosclerosis of the blood vessels of the gland; tuberculosis, syphilis or inordinate intake of alcohol. In one of the adult cases of Comfort *et al.* (1946) infestation by *Giardia lamblia* was considered as a possible aetiological factor but was finally discounted. On three of the occasions when the case of Collett and Kennedy was surgically explored what appeared to be a ruptured abscess of the pancreas was disclosed, and generalized peritonitis was also found on three occasions, the cause for this not being determined.

Case 17 of Comfort *et al.*, a boy of 12 years, had pancreatic ducts blocked by calculi with impaction in the head of the pancreas. The cause in the case of Davis and Kelsey, despite operation and biopsy, remained obscure and none of Opie's factors can be accepted as contributory in the present case.

Davis and Kelsey's patient had had mumps two

years before the onset of the pancreatitis, but no relationship to the pancreatitis could be established. No history of mumps was obtained in the present case and mumps virus antibodies were not present.

It is of interest that whereas, following operation, Davis and Kelsey treated their case with x-rays because of a report of nine cases of acute pancreatitis so treated by Morton (1945), and case 17 of Comfort *et al.* was similarly treated without apparent immediate benefit, in the present instance my patient received no special treatment, and resolution of the pancreatic affection proved very gratifying, although possible recurrences cannot be ruled out.

Summary

A case of chronic pancreatitis in a boy of 3 years of age is presented.

To the writer's knowledge this is the fifth and youngest case of chronic pancreatitis in childhood to be described.

The diagnosis, symptomatology and aetiology are discussed.

The patient was admitted to the Duchess of York Hospital for Babies under the care of Dr. S. K. Guthrie. Miss Pauline Gorse, of the Department of Biochemistry, Booth Hall Hospital, carried out the biochemical analyses.

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TORSION OF THE OVARY IN CHILDHOOD

BY

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Torsion of the ovary is uncommon in childhood and usually occurs as a complication of ovarian tumour (Higgins, 1950). Such tumours are rare in this age group (Fraser, 1926) and it was previously thought that most of them were malignant (Lyttle, 1940). Lanman, writing in 1929, could report only five cases among 12,260 children seen in the surgical service of the Children's Hospital at Boston, Mass., and Wakeley in 1933 reported that not a single ovarian teratoma (the commonest ovarian tumour) had been seen during the previous 25 years at The Hospital for Sick Children, Great Ormond Street, London, and only one each at King's College Hospital, London, and the Belgrave Hospital for Children, London, during the same period. In recent years an increasing number of these tumours has been recorded and the total now stands at a little over 200 (Costin and Kennedy, 1948). The present report describes two further examples of this condition and draws attention to the fact that, as a result of a better understanding of the pathology, many previously designated carcinomas or sarcomas were probably dysgerminomas or granulosa cell tumours.

Case Reports

Case 1. A schoolgirl aged 10 years was admitted to hospital on March 18, 1950, with a one week's history of abdominal pain. The family and social history was irrelevant.

One week before admission the patient developed, across the lower abdomen, a continuous pain with occasional colicky attacks. She remained in bed for two days and vomited several times but was well enough to get up for the remainder of the week. The day before admission the pain was localized in the right iliac fossa but on the day of admission it extended across the whole of the lower abdomen and was increasing in severity. Immediately before arrival at hospital she vomited three times; her bowels were open normally. There had been no diarrhoea, micturition was normal and there was no recent history of a cold or cough.

On admission the temperature was 98·6° F., pulse 88 and respiration 24. The child looked pale and ill. The general development, tongue, teeth and fauces appeared normal. Lymph nodes were palpable in the neck, axillae and groins.

There was tenderness and guarding in the right iliac fossa but no mass was palpable. Auscultation revealed normal bowel sounds. Per rectum a firm, smooth, tender mass was palpable in the pelvis. There was no vaginal discharge.

There were no other abnormal findings in the other systems. The urine was normal.

During the next 24 hours the pain persisted, the temperature remained normal but the pulse rate continued to rise. A provisional diagnosis of pelvic appendicitis or mesenteric adenitis was made and laparotomy was undertaken through a right lower paramedian incision.

There was a moderate amount of serosanguineous fluid in the peritoneal cavity. There was a tumour of the right ovary about 3 in. in diameter which, with the Fallopian tube, had undergone torsion and lay in the pouch of Douglas. The left tube and ovary appeared normal but the uterus was absent, its place being taken by a firm, fibrous cord about $\frac{1}{2}$ cm. in diameter. No other abnormality was discovered in the abdomen. A right salpingo-oophorectomy and appendicectomy was carried out. The interior of the vagina appeared normal on inspection but the cervix was tiny.

Convalescence was uneventful, and the child left hospital on the ninth day.

In June, 1951, there was no evidence of a recurrence, the breasts were just developing and there was a trace of pubic hair; the child was fit and well. In December, 1951, the child was fit, well and developing normally. She was not yet menstruating.

PATHOLOGICAL REPORT. Dr. J. K. Mason reported: The ' cyst ' was irregularly bossed and haemorrhagic in colour. It measured $75 \times 40 \times 60$ mm. On section it was seen to be a solid tumour with pale areas interspersed with large areas of haemorrhage. There was some attempt at lobulation visible. Between the tube and the ovary there was a small mass, size $27 \times 20 \times 15$ mm. of different appearance from the tumour, which contained small cysts.

Sample sections taken through the main tumour mass all showed the same picture of large cells with heavily staining nuclei and abundant pale cytoplasm separated into lobules by fibrous stroma. Mitoses were fairly numerous. There was considerable lymphocytic infiltration of the stroma. Large areas of frank haemorrhage

were present and the general structure was distorted by the changes following torsion. The appearances were those of an infarcted dysgerminoma of the ovary.

Section through the small mass below the tube showed a vascular structure almost completely replaced by

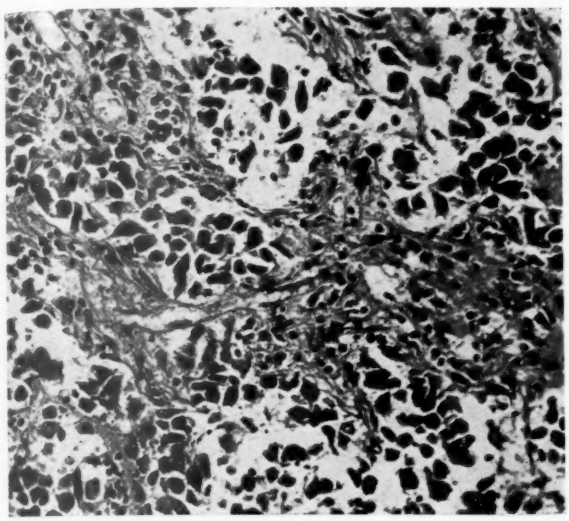

FIG. 1.—Photomicrograph of ovarian tumour removed from Case 1. The section shows fairly typical appearances of dysgerminoma (×175).

haemorrhage. The appearance indicated that this was a mass of broad ligament tissues altered by torsion. The tube was filled with haemorrhage and the epithelium destroyed.

The appendix, which was 80 mm. long and macroscopically normal, showed minimal haemorrhage in the submucosa and an exudate consisting of red cells and lymphocytes in the lumen. There was a small degree of early serosal inflammation.

Case 2. A schoolgirl aged 11 was admitted to hospital on May 5, 1950, with a three-day history of abdominal pain and vomiting.

For the first two days of the illness the child was constipated. On the third day she was still constipated and had left-sided abdominal pain. She was taken to another hospital where two enemas were administered and she was allowed to return home. On the fourth day she vomited twice. On the fifth day she was admitted to hospital; she vomited once.

On admission the temperature was 99·4° F., the pulse 104 and respiration 24. The child was intelligent and co-operative. The face was flushed, the tongue furred and foetor of the breath was marked.

The abdomen was scaphoid and moved poorly. There was hyperaesthesia over the right lower quadrant and generalized tenderness to deep pressure, most marked in the right iliac fossa. Per rectum there was tenderness on the right side.

There were no other abnormal findings. The urine was normal.

There were 20,000 leucocytes per c.mm. (polymorphs 80%, lymphocytes 10%, monocytes 10%).

A provisional diagnosis was made of an acutely inflamed appendix lying in the pelvis.

A lower right paramedian incision was made. There was no free fluid in the peritoneum. The omentum was normal, the appendix was exceptionally long but not inflamed and the small intestine showed no abnormality throughout its length. A mass was felt in the pouch of Douglas and on packing the intestines out of the way a pool of dark altered blood was seen. When this was mopped away, the mass was revealed as the left ovary and Fallopian tube, grossly oedematous and haemorrhagic. The ovary showed a small tear. The mass was

FIG. 2a

FIG. 2b

FIG. 2a and b.—Photographs of specimen removed from Case 2. Note the complete infarction of the ovary. A wedge of tissue has been removed for section. (Scale in inches.)

delivered into the wound and was found to have undergone torsion at the salpingo-uterine junction. The pedicle was clamped, ligatured and divided. The appendix was removed and the abdomen was closed in layers.

Immediately after operation the pulse rate was 150 but returned to within normal limits in 24 hours. Convalescence was uneventful and the child left hospital on the thirteenth day.

In December, 1951, the child was fit and well but not yet menstruating.

PATHOLOGY. Dr. J. D. Gray reported that blocks were made from different areas from a wedge cut from the ovarian tumour. The findings were the same in all sections.

A massive haemorrhage which had gone on to coagulation had torn its way through the ovarian architecture. There were not even cell islets or the remains of the stroma to be seen.

Discussion

Mayo and Butsch (1938) wrote: 'While comparatively rare, ovarian tumours occur with sufficient frequency among young girls to make it essential to keep the possibility in mind when dealing with abdominal symptoms', and then described the typical symptoms as being a mild, dull, recurrent pain with no nausea, vomiting or diarrhoea. In practice, however, the diagnosis is rarely made correctly except on those occasions when a tumour is palpable in the abdomen or pelvis.

The onset of torsion of an ovarian tumour almost always precipitates the signs and symptoms of an acute abdomen, although Lyttle (1940) reports the discovery at laparotomy of a benign ovarian cyst lying free in the peritoneal cavity of an infant of 2 months after spontaneous amputation of its pedicle at an unknown date. Torsion of a normal ovary appears to be excessively rare but has been reported by Fèvre (1949).

Simple cysts constitute 32% and dermoids, with which are included the teratomas, 24% of the ovarian tumours seen in infancy. The remaining 44% are made up of a variety of malignant or potentially malignant tumours: carcinomas, sarcomas, dysgerminomas and granulosa-cell tumours. When a child is seen with precocious development of the secondary sexual characters associated with a palpable mass in the pelvis, the diagnosis of granulosa-cell tumour of the ovary is almost certain.

Meyer (1931) was the first to describe the dysgerminoma, applying the name to solid carcinomatous ovarian tumours with a microscopic structure resembling that of seminoma of the testis and devoid of endocrine effects. These tumours are slower and less aggressive in growth (Willis, 1948) than testicular seminomas and they are sometimes cured by surgical removal. They do not appear to be very rare since by 1938 Novak and Gray were already able to collect 72 records and add a further 17 of their own. Three had occurred in children of 11 years or younger and attention was paid to their association with pseudohermaphroditism or sexual underdevelopment. There have been two reports of torsion of dysgerminoma in a child since 1938, by McNally (1945) and by Narat, Raider and Carton (1951). It is interesting that the child described (Case 1) should have no normal uterus although the vagina appeared to have developed adequately, and when she was seen recently she was apparently undergoing normal sexual development. Since the malignancy of this type of tumour is so variable, it was considered inadvisable to give deep x-ray therapy, especially as this would have destroyed the remaining ovary.

It is only possible to conjecture the type of ovarian tumour which occurred in Case 2 since it had been disorganized by the torsion of its pedicle and only a mass of organizing blood clot remained. A somewhat similar state of affairs was described by Schaeffer and Cancelmo (1939) and the diagnosis was presumed to be a cavernous haemangioma of the ovary. A recent review of ovarian tumours in childhood (Dargeon, 1949) pointed out that well over half of them were not malignant and therefore the prognosis in Case 2 may prove to be a favourable one. The child has so far shown no evidence of malignant disease and is developing normally.

Summary

Two cases of torsion of the ovary in children are described, presenting with the signs and symptoms of an acute abdomen.

The incidence of these tumours in childhood is briefly reviewed.

The prognosis is discussed and is shown to be more favourable than was previously supposed.

I am most grateful to Mr. E. V. Willmott, F.I.B.P., F.R.P.S. for the photomicrograph and to Mr. H. Daverson for the photographs of the tumour.

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THE SUCCESSFUL REMOVAL OF AN ANTERIOR MEDIASTINAL TERATOMA FROM AN INFANT

BY

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Teratomas of the anterior mediastinum are rarely discovered in children, and there are so far only a few reports of their successful removal. The youngest yet recorded is that of Vervat (1949) in an 8-month-old baby. The present case is thought to be of interest because of the age of the patient and the unusual pathological features presented by the tumour.

Case Report

The patient was a baby girl aged 8 days. Pregnancy had been normal and she was delivered at full term. As the mother had previously had a pelvic floor repair, delivery was by Caesarean section. The child was limp at birth, but responded slowly to lobeline and oxygen. The following day it was noticed that she became severely cyanosed after every breast feed and that the cyanosis was only slowly relieved by oxygen.

Examination showed her to be a healthy looking infant weighing 7 lb. 13 oz. No external abnormalities could be detected, but there was some indrawing of the lower intercostal spaces with respiration. Percussion of the chest revealed generalized dullness and there was poor air intake. There were no other abnormal physical findings.

A radiograph of the chest on the eighth day showed a large intrathoracic opacity filling most of the right hemithorax. The heart was markedly displaced to the left (Fig. 1). A right lateral radiograph showed that this opacity was situated almost entirely in the anterior mediastinum (Fig. 2). There were irregular areas of calcification in the anterior portion of the opacity. From the findings a diagnosis of anterior mediastinal teratoma was made.

During the next two days the cyanotic attacks following feeds became worse and it was decided to try and remove the tumour. The operation was carried out when the patient was 10 days old by Mr. Gordon Cruickshank. Before operation a blood transfusion was started. Anaesthesia was induced with oxygen and cyclopropane. The fifth rib was resected through a right subscapular incision. A tumour was visible immediately the pleura was opened. It occupied nearly the entire hemithorax, and was partly solid, partly cystic. Fluid was aspirated from the cystic part to diminish its bulk, after which the mediastinal pleura

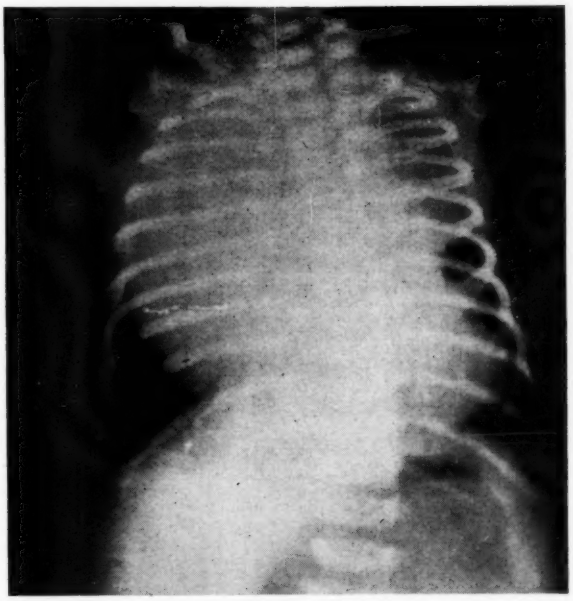

FIG. 1.—Antero-posterior radiograph of chest showing large right-sided mediastinal mass.

FIG. 2.—Right lateral radiograph of chest. Note areas of calcification in the anterior part of the tumour.

FIG. 3.—Radiograph taken six weeks after operation. Note regenerated rib.

overlying the tumour was incised and the tumour shelled out by finger without any difficulty. There was no bleeding and the lung inflated fully and easily. The chest was closed, using three layers of polythene thread and silk for the skin. Post-operative bronchoscopy was performed and the child's condition after operation was satisfactory.

The post-operative course was entirely uneventful. The baby could now take her feeds without becoming cyanosed, and the wound healed completely and rapidly. She was discharged eight days after operation. When seen six weeks later, she had gained weight and had no further symptoms. The lung was fully expanded and there was almost complete regeneration of the excised rib (Fig. 3). At 6 months the child's weight was 17 lb. 6 oz., and she was well in every respect.

FIG. 4.—Radiographs in two planes of the specimen. Note bone formation resembling digits in the upper one.

Pathological Report. Dr. D. B. Cruickshank reported on the tumour as follows:

The tumour measured 7×6×4 cm. and weighed 95 g. There was a solid mass occupying one pole, while the other end consisted of intercommunicating cysts. Related to one of the cysts was a small mass of solid tissue containing bone, cartilage, red mamillae and cartilaginous structures resembling incisor teeth; radiographs show that the bone in this area developed in linear fashion very suggestive of phalanges (Fig. 4).

Microscopically the following tissues could be seen in the cystic portion: thymus with Hassal's corpuscles; keratinized squamous epithelium; a myxomatous dermis with numerous hair follicles, hairs, sebaceous glands and fat cells; areas of well-formed cartilage; bone with red marrow; bundles of plain muscle; nerves; spaces lined with columnar ciliated bronchial epithelium; columnar mucous epithelium resembling intestinal type; lymphatic channels. In the solid portion of the tumour were structures resembling salivary glands. Some of these cells were relatively anaplastic and showed numerous mitotic figures. There were masses of primitive liver cells with distinctive Kupffer cells and surrounding blood; zones of neuroglia with numerous nerve cells; choroid plexus; primitive capillaries; intestinal epithelium with well-marked circular and longitudinal muscle; cardiac muscle; fat. Tissues of all embryonic layers occurred but voluntary muscle was absent.

The grouping of tissues was generally quite random but observed correlations included: (1) highly organized skin; (2) intestinal epithelium related to longitudinal and circular muscle; (3) cerebral tissues related to cartilage and bone; (4) ciliated epithelium, mucous glands, plain muscle, cartilage and bone were grouped together; (5) bone formations were not wholly erratic and some resembled radiographically bones of the hand (or foot).

Discussion

Teratomas of the anterior mediastinum are uncommon; of 82 teratomas studied by Willis (1948), only three occurred in that position. Rusby (1944) has reviewed the entire literature on anterior mediastinal teratomas since the first paper by Gordon in 1827 up to 1939, and was able to collect 245 cases; he adds six of his own. Laipply (1945) obtained the same figure in a review up to 1944. It has been possible to trace 120 cases reported since 1939. Of these only two have appeared in the British literature (Fawcett, 1944; Gardner, 1950). The increasing number of reports is undoubtedly due to the wider use of routine radiological examination; e.g. Schlumberger (1946) reported 16 cases in U.S. Army personnel out of several million men radiographed during military service. Many of these cases were asymptomatic.

These tumours occur at all ages, but are rarely discovered before puberty. The reason for this is twofold. Children are not often included in mass surveys, while teratomas tend to remain asymptomatic till after puberty. It has in fact been suggested that there is an antagonism between the growth of the tumour and that of its host, possibly due

to competition for some hormone. Nevertheless, several cases in young children do appear in the literature. Laipply mentions an anterior mediastinal dermoid in a stillborn infant. In Rusby's series the age was given in 174 and of these 17 were below 10 years. Heuer and Andrus (1940) state that 5·5% of 217 patients were below the age of 12. Of the present collection of 120 cases, the age was stated in five to be between 1 and 12 years (Berman, Powell and Hennessee, 1947; Fawcett, 1944; Heuer and Andrus, 1940; Maier, 1948; Rusby, 1944). Vervat (1949) reported the successful removal of a dermoid from a child of 8 months, the youngest case hitherto reported.

Teratomas have been defined by Willis (1948) as ' true tumours or neoplasms composed of multiple tissues of kinds foreign to the part from which they arise '. This definition applies equally to dermoids; they will therefore be considered together here.

The pathological report revealed that the tumour was a teratoma of unusual complexity. The tissues most commonly found in these tumours are skin, teeth, nervous and lymphoid tissue and mixed glandular structures. On the other hand, liver is rare and the presence of cardiac muscle seems only to have been reported twice before (Katsurada, 1901; Schlumberger, 1946). The latter reports the presence of cardiac muscle in a malignant teratoma, and that tissue was also found in a liver metastasis.

Histologically, the tumour was highly differentiated. The degree of anatomical differentiation, however, was poor, but certain tissue relations were observed, e.g., intestinal epithelium related to longitudinal and circular muscle, cerebral tissue related to cartilage and bone. Similar relations between tissues have frequently been reported and comment has been made on them by several authors. Willis mentions the relationship between masses of central nervous system tissue, cartilage and bone and between ciliated epithelium and cartilage, and points out the frequent occurrence of lymphoid tissue in the ' submucosa ' of ' intestinal ' structures. Similar tissue relations are mentioned by Schlumberger, and Needham (1942) goes so far as to state: ' Almost all smooth muscle in teratomas is clearly associated with glandular cavities. The impression is given that the development of muscle is determined by the presence of epithelium.'

The presence of definite tissue relations in teratomas appears to be fairly constant. It must be explained by any attempt to account for the origin of these interesting tumours, and may in turn provide the clue to such an attempt. It suggests that even amongst the chaos of the teratoma, some degree of control over the tissues exists. This is exercised by the influence of one tissue over another, so that these tissues still possess some ability to shape the destiny of their neighbours, a phenomenon known to the embryologist as dependent differentiation. It seems likely then that a study of normal developmental mechanics will further our understanding of the origin of the teratoma.

In recent years a great deal of work has been done on the control of growth and differentiation in the embryo; an outline of this work is given by Needham (1942). It has been shown that differentiation occurs as a result of the action of specific, hormone-like, chemical substances produced by the various embryonic tissues on cells capable of reacting to these substances. The earliest of these substances is produced by the dorsal lip of the blastopore and induces the formation of a neural axis in neighbouring tissues. This substance, known as the primary organizer, has been found to occur in practically all tissues so far examined, embryonic and adult, and can be liberated by killing the cells and denaturing their proteins. It appears to be a steroid related chemically to the sex hormones and some of the carcinogenetic hydrocarbons. The primary organizer can only produce induction of a neural axis on cells at a certain stage of their development, when they are competent to react. Further, not all cells possess the ability to form a neural axis showing regional differentiation. The ability of a tissue to undergo regional differentiation under the influence of an organizer is known as individuation. The nature of the individuation process is not yet understood. Once a neural axis is established it in turn produces substances capable of inducing differentiation in neighbouring tissues. Thus, a series of secondary and subsequent organizers have been shown to occur. Examples are the induction of the lens by the optic cup, and the production of the cartilagenous auditory capsule by the nervous elements of the ear vesicle. The latter recalls the observed correlation between cartilage and nervous tissue in teratomas.

There are then three factors essential for normal organogenesis; the organizer, tissue competence to react, and individuation. The first two acting together call into being tissues, while the third imparts to them their proper regional characters. Needham expresses his belief that ' what lies behind the strange phenomena seen in the teratoma is the failure of the individuation field, at some point early in development, to control the action of the evocating substance '. It seems possible that

excessive production of evocator substance may bring about such a failure in individuation. Teratomas can be produced in the cock's testes by the injection of zinc salts; these are known to cause denaturation of proteins and thereby release of organizer. Its action on germinal cells may produce chaotic tissue proliferation.

Schlumberger has extended this concept and advanced an ingenious explanation for the occurrence of teratomas in the anterior mediastinum. He, like Collenberg (1869), points to the close relationship of the anterior mediastinal teratomas to the tissues derived from branchial structures. Of these, the thymus '*Anlage*' regularly descends into the anterior mediastinum. It contains in close relationship ecto- and endodermal structures, as well as Hassal's corpuscles whose origin is still doubtful. He suggests that degeneration of Hassal's corpuscles releases organizer which acts on embryonic cells present, causing their chaotic multiplication in the same way as zinc salts cause chaotic cell growth when injected into the cock's testes. Schlumberger concludes that 'teratoma of the anterior mediastinum may be identified more precisely as teratoma of the thymus'.

This theory accords best with the facts of experimental embryology. Many others have been propounded and accounts of them can be found in the writings of Willis and Schlumberger. They seem less firmly based on observed fact and will not be discussed here.

Conclusion

The point which emerges from the case here reported is that thoracotomy should not be withheld where symptoms require it simply because of the age of the child. Thoracotomies have many times been performed on infants and are on the whole well tolerated. Thus, Gross (1946) has reported a pneumonectomy on a child 3 weeks old, and Twente (1950) removal of an intrathoracic tumour in a child aged 10 weeks. In the present instance the danger of leaving the tumour, in view of the progressively severe symptoms, was considered greater than the danger of operative intervention.

Summary

A case of anterior mediastinal teratoma causing symptoms in a child aged 10 days is reported. It was successfully removed with recovery of the patient. The pathogenesis is briefly discussed and a review of the entire literature on the subject since 1939 is included. A bibliography is also given.

My thanks are due to Mr. Gordon Cruickshank for permission to publish this case, and to Dr. D. B. Cruickshank for allowing me to make use of his pathological report.

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HAEMATOGENOUS OSTEITIS OF INFANCY

BY

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During the past 30 years there has been much contradictory literature on haematogenous osteitis in infancy (Thomson and Lewis, 1950). In infancy the disease differs in so many respects from osteitis in older children that a separate consideration of haematogenous osteitis in children under 2 years of age is desirable. Even in this limited age group we must consider the disease under two headings: (1) streptococcal osteitis of infancy and (2) osteitis of the newborn.

Streptococcal Osteitis of Infancy

The differences between streptococcal osteitis of infancy and acute osteitis in older children have been emphasized by many authors, notably Paschlau (1933), Green (1935), White (1937), Compere, Schnute and Cattell (1945) and Blanche (1952). In this form of osteitis severe toxaemia is unusual and abscess formation and joint infections are common—probably due to the thin and porous infantile cortex and delicate epiphyseal cartilage. Sequestrum formation is rare and any sequestra are usually absorbed spontaneously. Bone deformities are quickly rectified by growth and full joint function is restored early. Even before the introduction of antibiotics, these cases responded well to minor surgical intervention (Dennison, 1948). In the communication from which this statement is taken streptococcal infection of bone is described under the heading of 'subacute osteitis'. The prime consideration in these cases is treatment of the systemic upset and not the local bone lesion. Early drainage does not decrease the amount of bone destruction nor does it limit systemic manifestations. Although these infections have been classed as subacute, poorly-timed surgical intervention may jeopardize the child's life.

Since the introduction of penicillin therapy in bone infections during 1945, 19 cases of streptococcal osteitis of infancy have been treated in one unit of the Royal Hospital for Sick Children, Glasgow. All made a complete and uneventful recovery.

Osteitis of the Newborn

Although it is not a common condition, osteitis of the newborn is well known. Fraser (1924) stated that the disease was almost always fatal, whereas Dillehunt (1935), Cass (1940) and Stone (1942) regarded the disease as benign and all three gave a good prognosis for life and function. The confusion has been largely clarified by Greengard (1946) and Thomson and Lewis (1950). These authors pointed out that there were two forms of the disease, one benign and one severe.

Since 1945, 109 cases of acute haematogenous osteitis have been treated in one unit of the Royal Hospital for Sick Children, Glasgow. In all but two cases the infecting organism was a coagulase-positive staphylococcus. (Infections due to the pneumococcus and streptococcus each occurred once.) In this series seven patients were in the neonatal age group and in this group all infections were staphylococcal. During this period many examples of subacute osteitis (Dennison, 1948) were treated in the unit. Among these were 12 examples of the benign form of neonatal osteitis. In this group the infecting organism was a coagulase-positive staphylococcus in 10 cases and a haemolytic streptococcus in two.

In its benign form neonatal osteitis affects only one bone, there is little systemic upset, and even before the introduction of chemotherapy and antibiotics the prognosis was good. In the present series of staphylococcal infections the disease affected the maxilla (four cases), clavicle (one case), humerus (two cases), femur (two cases) and calcaneus (one case). In all cases recovery was complete and without deformity although the staphylococcus was resistant to penicillin in five cases.

The severe form of neonatal osteitis is also known as generalized osteitis of the newborn. The infection is systemic and several bones may be involved with multiple swellings of the extremities (Athanassiadis, 1951). The diagnosis is confirmed by blood culture and by radiographic changes. There is a marked tendency to early infection of

FIG. 1

FIG. 2

FIG. 1.—Radiographic appearances four weeks after the onset of neonatal staphylococcal osteitis. Subperiosteal new bone is seen in the upper third of shaft and also severe damage to the lower metaphysis and epiphysis of the right femur.

FIG. 2.—At the age of 5 years the x-ray film shows shortening of the femur and gross deformity of the lower articular surface of the right femur.

joints but in some cases there is surprisingly little deformity or disability following the joint infection. Any deformities which do occur are due to damage to the articular ends of the bones and not to adhesions in the joint. Generalized osteitis of the newborn is less common than the benign form and before the introduction of antibiotics the outlook was always grave. It is possible that some cases included in the 'benign' group would have progressed to the severe form if they had not been treated with antibiotics. Seven patients with the severe type of neonatal osteitis have been seen since 1945. All were gravely ill when first seen.

Case Reports

Case 1. A girl, well until 2 weeks old, was admitted with swelling of both thighs and the right knee. Blood culture grew coagulase-positive staphylococci. (The sensitivity of the organism to penicillin was not estimated.) Penicillin was given by intramuscular drip in a dose of 100,000 units daily for 11 days (total 1·1 mega units). A soft tissue abscess of the right thigh was aspirated and pus was aspirated from the right hip and knee joints. Radiography revealed new subperiosteal bone over the shafts of both femora. Four weeks after the onset of the illness there was evidence of destruction of the right lower femoral epiphysis (Fig. 1). There was a subsequent interference with growth of the right leg, and five years after the onset of osteitis there was 3 cm. shortening and gross deformity of the articular surfaces (Fig. 2). Movements of the knee joint are still free and painless.

Case 2. A boy developed a paronychial whitlow of the left thumb and right index finger six days after birth. Two days later there were red tender swellings of the left arm, right thigh and both legs. Arthritis developed in both knees and coagulase-positive, penicillin-sensitive staphylococci were grown from the aspirated fluid. Radiography showed that periosteum was raised over the left humerus and left radius and lesions in the metaphysis of the lower left femur and upper left tibia. Penicillin, 1·5 mega units, was given by intermittent intramuscular injection in eight days. Parotitis developed on the third day but none of the swellings was aspirated and the infant's condition ceased to give rise to anxiety after the fourth day of treatment. Recovery was complete with resolution of all bone lesions and recovery of complete movement of both knee joints.

Case 3. A boy was admitted at the age of 3 weeks with a tentative diagnosis of infantile cortical hyperostosis. There was a firm red swelling over the left clavicle, swelling of both thighs and right leg and effusion in both knees. Radiography revealed osteitis of the left clavicle (Fig. 3), an area of rarefaction in the right ilium and periostitis of both femora with effusion in both knee joints. Penicillin was administered in a dosage of 20,000 units three-hourly by intramuscular injection. After two days the clavicular swelling became fluctuant and it was aspirated. The temperature continued to fluctuate. Culture of the pus revealed a coagulase-positive staphylococcus, resistant to penicillin but sensitive to streptomycin and aureomycin. On receipt of the report penicillin therapy was stopped and the infant was given 25 mg. aureomycin six-hourly. After 24 hours the temperature became normal and the child's condition improved rapidly. After seven days the hospital supply of aureomycin was exhausted and penicillin therapy was restarted with a dose of 50,000

FIG. 3.—Osteitis of the left clavicle.

units four-hourly. Within 24 hours the temperature was again elevated. The knees were aspirated but irregular pyrexia continued until aureomycin became available five days later. Two weeks after admission a large intrapelvic abscess was evacuated. Both knees

FIG. 4.—Radiography shows lesion in right ilium and gross arthritis of knees with bone destruction at lower end of both femora.

FIG. 5.—Gross destruction of lateral aspect of lower right femur and medial aspect of the lower left femur.

were aspirated on four occasions and all specimens revealed a penicillin-resistant staphylococcus. During the fourth week of treatment the temperature became normal and thereafter the patient's general condition improved rapidly. Four weeks after admission radiography revealed gross arthritis of both knees with bone destruction and partial subluxation (Fig. 4). The infant was discharged after 14 weeks. At the age of 8 months movement of both knees was full and free but radiography revealed gross damage to the ends of both femora (Fig. 5). It is still too early to give anything but a guarded prognosis on future bone growth and final joint function.

Case 4. A boy was well until 3 weeks of age when he developed diarrhoea. He was treated at home for

FIG. 6 FIG. 7

FIG. 6.—Extensive osteitis of tibia.

FIG. 7.—Extensive involucrum formation and gross destruction of the left tibia six months after onset.

a week with rectal chloromycetin. The diarrhoea improved but his general condition deteriorated and he developed a red swelling over the right shoulder. He was admitted to hospital with a generalized rash and all the features of septicaemia. There was gross swelling of the entire right leg and pus was aspirated from the right knee joint. Coagulase-positive staphylococci were grown from the blood, from the urine, from a rectal swab and from the knee joint fluid. Aureomycin, 100 mg., was given intravenously and thereafter orally in a dose of 25 mg. six-hourly. Radiography revealed oedema of the soft tissue of the leg but no bone lesion. The staphylococcus was reported sensitive to streptomycin and aureomycin but resistant to penicillin. Four days after admission the left knee was aspirated. The staphylococcus isolated from the fluid was reported sensitive to penicillin. Two days later a small subperiosteal abscess over the head of the tibia was evacuated and the wound sutured. The organism was reported sensitive to streptomycin and moderately sensitive to aureomycin. On the eighth day the general condition had improved and the temperature was normal. Aureomycin was discontinued. As the haemoglobin was only 65%, a small blood transfusion was given. The child remained well until the thirteenth day when the temperature rose to 103° F. and he once more became seriously ill. Signs of bronchopneumonia appeared and were confirmed by radiography.

FIG. 8

FIG. 9

FIG. 10

FIG. 11

FIG. 8.—Photograph showing discoloration and swelling of left lower limb and right arm. Child toxic and marasmic.

FIG. 9.—Osteitis of left tibia.

FIG. 10.—Radiography shows free sequestrum two months after onset.

FIG. 11.—Radiographic appearances four weeks after sequestrectomy showing early consolidation of tibia.

Radiographs also revealed extensive osteitis of the tibia (Fig. 6). Aureomycin therapy was begun again in a dose of 50 mg. six-hourly. The general condition slowly improved and after the nineteenth day the temperature remained normal. Aureomycin was discontinued on the twenty-sixth day. The child was dismissed from hospital after three months. Six months after the onset of the illness radiography showed extensive involucrum formation and gross destruction of the left tibia (Fig. 7). Movement of the knee joint was full and painless.

The child was re-admitted three months later with persistent pyuria. Radiography revealed multiple calculi in the left kidney. Several stones were removed but kidney function remained poor on that side and eventually the kidney was removed. The pathologist reported chronic pyelonephritis with multiple calculi. The child made a rapid recovery from the nephrectomy but he will probably require sequestrectomy at a later date.

Case 5. A boy was well until 3 weeks old, when he developed a left inguinal abscess. This was incised but the pus was not examined. Three days later the left leg was red and swollen and on admission to hospital the following day the right arm was also red, hot and swollen (Fig. 8). He was marasmic and suffered from a toxic gastro-enteritis. Penicillin, 50,000 units, was injected intramuscularly and pus was aspirated from the right arm and left leg. Penicillin was continued in a dose of 25,000 units three-hourly. The organism proved to be a coagulase-positive staphylococcus, resistant to penicillin but sensitive to streptomycin and aureomycin. On receipt of this report two days after admission, penicillin was discontinued and oral aureomycin was given in a dose of 50 mg. six-hourly. The infant was now gravely ill with deep jaundice and enlargement of the liver and spleen. Three days after admission pus was aspirated from a whitlow of the left index finger. After four days of aureomycin therapy, the general condition began to improve, vomiting and diarrhoea had ceased, and the infant showed more interest in his feeds. Radiography showed infiltration of both lung fields and soft tissue swelling of the right arm and left leg. Ten days after admission jaundice was fading but there was gross swelling of the left knee. Pus was aspirated from the knee joint and streptomycin instilled. Two days later there were pyaemic lesions of the fifth left finger, the right palm and the right wrist. Pus was aspirated from each site. Radiography at this time revealed osteitis of the left tibia (Fig. 9) and an area of translucency in the neck of the right radius. Following our experience with Case 4 aureomycin was continued for four weeks. Radiography at this time revealed

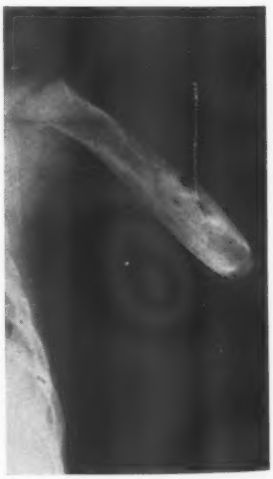

FIG. 12.—Radiographic appearance of left humerus at age of 6 months.

healing lesions of the right radius and proximal phalanx of the left index finger and extensive osteitis of the left tibia. Two months later a radiograph revealed a free sequestrum (Fig. 10). Sequestrectomy was performed and a subsequent radiograph showed the tibia consolidating (Fig. 11).

At the age of 5 months the child reported with a painless swelling over the left deltoid. The swelling was superficial and radiography revealed no bone lesion. Aspiration revealed a coagulase-positive staphylococcus, resistant to penicillin but sensitive to aureomycin. Radiography two weeks later showed extensive osteitis of the left humerus (Fig. 12). The general condition remained excellent but a month later he was re-admitted with a painless superficial swelling of the upper left thigh. Radiography revealed early osteitis of the left ilium. Aureomycin therapy was begun and the abscess was aspirated and 0·25 mg. of aureomycin in a glycine diluent was instilled. The coagulase-positive staphylococcus grown from the pus was reported resistant to penicillin but sensitive to aureomycin and chloromycetin. The child is still under treatment.

Case 6. A girl became cross and fevered, with loose stools, at the age of 3 weeks. (A week previously the umbilical cicatrix had been mildly infected.) The child became gravely ill and she was treated at home with oral chloromycetin. At 4 weeks of age the right leg became swollen and this swelling slowly subsided until it became localized over the right ilium two weeks later. Radiography revealed early osteitis of the right ilium. The general condition was not satisfactory: 8 ml. of thick pus was aspirated and 0·5 g. streptomycin instilled. The coagulase-positive staphylococcus grown from the pus was reported resistant to penicillin but sensitive to aureomycin and chloromycetin. Oral chloromycetin was discontinued after four weeks and radiography at this time revealed extensive osteitis of the ilium (Fig. 13). A week later the swelling over the right ilium recurred. The child was admitted to hospital and aureomycin therapy was begun. Marrow puncture revealed a penicillin-resistant staphylococcus, and 0·1 g. aureomycin in a glycine diluent was instilled into the marrow. Marrow puncture and instillation of aureomycin was repeated a week later. A scanty growth of a coagulase-positive staphylococcus was reported. The infant is still under treatment. The general condition remains satisfactory but there is gross thickening of the ilium.

Case 7. At the age of 3 weeks this boy was admitted to a fever hospital suffering from gastro-enteritis. He was treated with 50,000 units of penicillin four-hourly and dextrose and plasma by intravenous drip. After two weeks an abscess appeared at the site of the cut-down in the right leg. *Proteus* was grown from the aspirated pus. A week later the left knee became swollen and aspiration revealed a coagulase-positive staphylococcus resistant to penicillin but sensitive to aureomycin. The infant was transferred to this hospital. On admission he had gross swelling of the left knee and fullness and limitation of movement of both hips. Aureomycin therapy was begun. Radiography revealed arthritis of the left knee and osteitis of the upper ends of both femora (Fig. 14). Both hip joints and the left knee joint were aspirated and 0·25 g. streptomycin instilled. Marrow fluid was aspirated from both upper femoral metaphyses. The fluid from all three joints was reported sterile, but marrow fluid showed a coagulase-positive staphylococcus resistant to penicillin and aureomycin but sensitive to chloromycetin. The limbs were immobilized in abduction to prevent subluxation of the hips. Aureomycin was discontinued and chloromycetin substituted in a dose of 50 mg. six-hourly.

The child is still under treatment. Already it appears that irreversible damage has been done to the upper end of the left femur.

Discussion

Acute haematogenous osteitis occurs most commonly between the ages of 2 and 12 years and the causal organism is a coagulase-positive staphylococcus in 95% of cases (White and Dennison, 1952). In a series of 212 cases of acute osteitis treated in one surgical unit between 1936 and 1950 only seven infections were due to a streptococcus.

FIG. 13.—Radiographic appearance of the right ilium showing extensive osteitis at the age of 8 weeks.

FIG. 14.—Radiograph shows osteitis of upper ends of both femora and arthritis of hips and subluxation of left hip.

There were three pneumococcal infections and the remaining 202 cases were caused by a staphylococcus. While pyogenic bone infection is not uncommon in the first two years of life, the infecting organism is commonly a streptococcus. These infections are relatively benign and only rarely endanger either life or limb. Streptococcal osteitis of infancy should be classed as subacute osteitis (White and Dennison, 1947).

Osteitis of the newborn is almost invariably staphylococcal. Although it has already been stated that the disease presents in either a benign or a severe form, it may be impossible in the early stages to foretell which course the disease will take. Since 1946, 17 cases of staphylococcal osteitis of the newborn have been treated in the unit. In 10 the organism was resistant to penicillin. In 102 cases of acute staphylococcal osteitis in older children treated during the same period the organism was sensitive to penicillin in all but one case. Of the neonatal cases, 10 were benign, and although the staphylococcus was resistant to penicillin in five, the general condition of the patient never gave rise to anxiety and all made a full recovery. Seven cases of severe neonatal osteitis have been reported in some detail. The systemic infection was grave in all seven. In Case 2 the staphylococcus was sensitive to penicillin; in Cases 3 to 7, it was penicillin-resistant. Sensitivity was not assessed in Case 1, but, from the gross bone damage which occurred in spite of penicillin therapy, it is possible that the staphylococcus in this case was penicillin-resistant.

In Glasgow the incidence of acute haematogenous osteitis in childhood remained almost constant during the period 1930-1949 (White, 1937; Dennison, 1948). During the past 18 months, however, the disease has become exceedingly rare. Yet five cases of neonatal osteitis of the severe type have been treated in the unit during the past year. The causal organism in all five was a penicillin-resistant staphylococcus.

It is now our practice to assume that all neonatal staphylococcal infections are caused by a penicillin-resistant organism and to administer aureomycin from the beginning of treatment. Should the organism be reported penicillin-sensitive, aureomycin can be stopped and treatment continued with the more readily available penicillin. Following our experiences with Cases 3 and 4, we now give aureomycin for a much longer period than is usually recommended. A minimum period of three weeks is considered essential in any case of generalized osteitis of the newborn. As with penicillin therapy, neither the general condition of the patient with osteitis nor the temperature chart are reliable criteria for cessation of therapy (Dennison, 1948). As penicillin is bacteriocidal and aureomycin and chloromycetin are bacteriostatic, it is probably even more dangerous to stop aureomycin and chloromycetin treatment too early. No ill effects have followed prolonged courses of aureomycin or chloromycetin. And now in Case 7 we are faced for the first time with the problem of dealing with an organism which has apparently become resistant to aureomycin.

Subperiosteal and soft tissue abscesses should be evacuated using a wide-bore needle. This must be done before increased tension leads to necrosis of the overlying skin. As in older children, joint infection is treated by aspiration followed by penicillin instillation. This procedure is repeated as required. When the organism is resistant to penicillin, streptomycin or aureomycin in a glycine diluent is instilled into the joint instead of penicillin.

While the percentage recovery to full function in cases of osteitis of childhood is gratifyingly high, the results in neonatal osteitis can be as bad as anything one experienced before the introduction of antibiotics. One can only presume that in the past such cases died of septicaemia before gross damage to bone and joint became apparent. Although the antibiotics are life-saving, irreversible damage is done to the bone in the early stages of the disease and the progress of the bone disease is influenced little by antibiotic therapy. There is gross deformity of the limb in Case 1; there will be serious deformity in Cases 3 and 7; the prognosis is still guarded in Cases 4, 5 and 6. Case 2 should probably be included in the 'benign' group.

Summary

Osteitis in infancy differs from osteitis in older children.

The disease as it affects children under the age of 2 years falls into two groups: (1) streptococcal osteitis of infancy; (2) osteitis of the newborn. In both types joint infection is common but sequestrum formation is rare. Poorly timed surgical intervention may jeopardize a child's life.

Streptococcal osteitis of infancy is generally a mild disease.

Osteitis of the newborn appears in a benign and in a severe form. The infection is usually staphylococcal.

In 102 patients with acute osteitis over the age of 2 years, there has been only one penicillin-resistant infection. In 17 cases of staphylococcal osteitis in the neonatal group, the organism has been resistant to penicillin in 10 cases.

Seven cases of neonatal osteitis of the severe type are reported.

The treatment of staphylococcal arthritis by aspiration and instillation of penicillin gives satisfactory results when the organism is sensitive to penicillin. Streptomycin or the intravenous dosage of aureomycin may give equally good results when the organism is penicillin-resistant.

It is suggested that in the treatment of osteitis with aureomycin and chloromycetin the course should be longer than is usually recommended.

In the severe form of neonatal osteitis the diagnosis is rarely made before irreversible bone damage has taken place. Although the mortality is now low, the morbidity is still high.

The cases were all treated in Mr. Matthew White's wards and we thank him for his advice and encouragement. We also thank Dr. A. M. MacDonald and his staff in the pathology department for their constant help. The photographs and reproductions of x-ray films are the work of Mr. J. L. A. Evatt, A.R.P.S.

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RADIOGRAPHS OF THE HAND AS AN INDEX OF SKELETAL MATURITY IN INFANTS

BY

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We are indebted to the late Professor Wingate Todd (1937) and his colleagues for the concept of skeletal maturation as a specific entity in the growth process. It has long been known that hypothyroidism is a potent cause of retardation in the maturation process. Francis (1939) and other authors in the Brush Foundation group have shown that any infection or feeding difficulty may hold back normal progress towards skeletal maturity. It is the purpose of this paper to review the histories of nine skeletally retarded 1-year-old children seen in the Oxford Child Health Survey.

Material

The children followed in the Survey were born in Oxford between 1944 and 1948 and recruited from municipal infant welfare centres and a private clinic. They were 580 in number, and the social class grouping (Registrar-General, 1911) was as follows:

TABLE 1

Social Class	Percentage
I	5·3
II	10·17
III	66·8
IV	10·17
V	7·59
Unoccupied	0

Selection of Cases

The osseous centres for capitate and hamate are visible by radiograph in both sexes by 6 months of age (Davies and Parsons, 1927; Paterson, 1929). Modern authors maintain that these bones are radiologically visible in the hand of the average girl at 2 months and the average boy at 3 months (Francis and Werle, 1939; Pyle and Sontag, 1943). It was therefore decided that the absence of either of these bones in either hand at the age of 1 year could be taken as an indication of skeletal immaturity. Of the 580 children in the Survey, an antero-posterior radiograph of each hand was taken in 561. Eight fell into the group defined above as immature. Six were boys, and two were girls. Since girls mature more quickly than boys (Flory, 1936; Pryor 1923) this distribution is to be expected. In addition a girl whose hamates and capitates were so rudimentary as to be only visible on the closest scrutiny of the x-ray plate has been included. The nine cases will be referred to as the selected group, and the 561 children from whom they were picked as the survey group.

The only routine radiographs other than of the hands, which were taken of all the children, were antero-posterior films of the knees and chests. The chest is, of course, of no help in accurately assessing skeletal age. Although the knees of all the nine selected children were rather more retarded than the mean of the survey group, in one case alone (Case 8) was the retardation really gross. This child was a cretin.

Data

Cretinism. One child (Case 8) was the most backward of the nine, and was found at the age of 1 year to be a cretin. Radiographs gave the lead to the diagnosis, which was substantiated by clinical appearances. Until this time the mother was quite unaware that anything was wrong with her girl, for in spite of frequent visits to the clinic, the diagnosis had not been obvious to the physicians. She yielded immediately to thyroid therapy and at the age of 5 had an intelligence quotient of 100.

Obstetric. All the children were delivered normally. Apart from the minor ante-natal and post-natal complaints listed in Table 2, the mothers had good health. Although the mother in Case 6 had had rheumatic fever as a girl, she had no history of cardiac involvement at any time. Apart from the child in Case 5, who was born at home, and in Case 3, who was born in an institution run by the Oxford City Health Department, all the babies were born in maternity departments of the Oxford hospitals. Birth was three weeks premature in Case 6, and was three weeks after the expected

TABLE 2

OBSTETRIC AND CLINICAL DATA

	Case No.	Date of Birth	Obstetric History				Illnesses and Operations	Congenital Abnormalities	Clinical Assessment	Preventive Vaccinations and Inocculations
			Ante-natal	Post-natal	Birth	Parity of Mother				
Males	1	9.1.46	Normal	Normal	Full term	1	Circumcision, 2/12 ? Measles Slight diarrhoea and vomiting 11/12		Good and alert	
	2	29.1.46	Heartburn and backache	Normal	Full term	3		Umbilical hernia	Good and alert	Smallpox
	3	25.5.47	Normal	Normal	? 3/52 Post-mature	1	Pemphigus neonatorum, 1/52	Umbilical hernia Slight strabismus	Flabby and happy	Diphtheria
	4	29.7.48	Normal	Pale, easily tired	Full term	1			Good and alert. Interested in everything	
	5	2.10.46	Normal	Normal	Full term	2			Good, only content when lying	
	6	24.1.46	Rheumatic fever, aged 12	Pale, depressed	3/52 Premature	1	Physiological jaundice. Slight facial palsy	Umbilical hernia Slight strabismus	Physique and mentality fair; alert	Diphtheria
Females	7	22.6.45	Normal	Normal	Full term	1	Tonsillitis, 9/12 Slight diarrhoea and vomiting 10/12	Pilonidal sinus Umbilical hernia Pigmented naevus	Thin; mentally alert	
	8	1.1.46	Normal	Tired, backache	Full term	1	Cretinism diagnosed at 1 year	Umbilical hernia	Flabby; lethargic	
	9	3.3.47	Bad, vomiting at first	Normal	Full term	1	Diarrhoea, 12/12		Good and alert	Smallpox Diphtheria Whooping cough

date of delivery as calculated by the mother's last menstrual period in Case 3.

Illnesses. The premature child (Case 6) was detained in the Radcliffe Infirmary, Oxford, for the first month of his life because of physiological jaundice. On his visits at 3 and 6 months of age he was described as a good, contented baby. On his fifth visit, aged 12 months, he was just recovering from a cold and had impaired air entry in both lungs.

One child (Case 1) was said by his mother to have had measles when 2 months old, but it is not certain that there were grounds for this diagnosis.

One child (Case 3) had pemphigus neonatorum in the first week of life. However, the complaint quickly yielded to penicillin.

Apart from a setback in her tenth month, when she had tonsillitis with slight diarrhoea, the health in Case 7 was excellent.

Umbilical Hernia. Five of the nine selected children (55%) had umbilical hernias. This is similar to the figure of 53% for the whole survey group.

Milestones. The children all achieved the usual milestones of the first year (Table 3). Some were precocious; Case 9, a girl, was walking at 8 months, and Cases 4 and 5 were repeating words before the age of 12 months.

Teeth. Apart from the cretin only two of the children had no teeth at 1 year. In the rest of the survey group it was found that 6% of the girls and 7% of the boys were edentulous at this age. One of the selected children (Case 5) had 13 teeth. Only 6% of the survey group of boys and 4% of the survey group of girls had this number or more at a year. The other five selected children had four to six teeth at 12 months. This compares favourably with the mean of four to five teeth at this age for the whole survey group.

Fontanelle. Two children (Case 2 and Case 8, the cretin) had fontanelles at 1 year of age unusually widely open for their age. The others fell well within normal limits. In the survey group no correlation has been found between closure of the fontanelle and hand maturity.

I.Q. at 5 Years of Age. Five of the children remained in the survey group until they reached the age of 5. Of these only one, Case 7, had an I.Q. of less than 100 on achieving this age. The Terman-Merrill revision of the Stanford-Binet test, Form L, was used.

TABLE 3

GENERAL DEVELOPMENT

Case No.	Missing Bones in Hand	Milestones						No. of Teeth at 1 year	Fontanelle (Finger-breadths at 1 year)	I.Q. at 5 years
		Head Up	Hear and See	Sit	Crawl	Stand	Other			
		Age (in months)								
1	Left hamate		No record			12		0	2	108
2	Right capitate	3	6	5	9		Drinks unaided, 12	4	½	107
3	Right hamate	3		5	12	12		4	1	
4	Both hamates	2	3	9	11		Words, 12	4	Closed	
5	Right capitate	3		8	22		Words and drinks, 11	13	1	108
6	Both hamates		No record					0	Closed	
7	Right hamate	2	3	7	8	9		6	½	94
8	All bones	3	6					0	2	100
9	Four very primitive bones only	3	6			8	Walked, 8 Feeds self, 12	6	1	

Weight. It will be noted that two of the full term babies (Cases 4 and 7) were very light at birth, each weighing 5 lb. 1 oz. The premature child (Case 6) weighed 6 lb. 1 oz. The average weight of the selected boys was 14 oz. less than the average for all the boys in the survey group. This figure is almost twice its standard error, and indicates a significant difference between the two male averages. Since there are only three girls in the selected group, the standard error of the difference between the selected and general female averages is much larger. Therefore, although the difference observed is the same as it is for the males it is not statistically significant. However, the tendency for the immature girls to be light at birth is clearly seen.

Since the weight range at 1 year is greater than at birth, the differences between the averages at 12 months (20 oz. for males and 19 oz. for females) are too small to be considered significant.

Feeding. Case 1 was the only one which was not breast fed for at least four months. No feeding troubles were experienced by this child or any others. The proportion breast fed (88%) is much higher than the figure of 53·8% for the survey group children who were breast fed for at least four months.

Social Background. The mother's estimate of the amount of money spent per adult per week is included in Table 5. In considering these figures allowances must be made for individual miscalculations, and for the fact that these estimates were made in 1949, before the sharp rise in the cost of living. The mean expenditure in all the homes under survey was 15/6d.; in this small group it is approximately 22/6d.

Seven of the children came from homes of Social Class III (Table 1).

TABLE 4

WEIGHT

		Birth Weight (lb. oz.)	Weight at 12 Months (lb. oz.)
Males	1	6 12	21 7
	2	7 1	20 14
	3	7 15	22 14
	4	5 1	20 15
	5	8 0	21 2
	6	6 1	20 0
Average		6 13	21 9
Average for all males in survey group		7 11	21 13
Difference between averages with standard error		−14 oz. ±7½	−20 oz. ±15½
Females	7	5 1	16 0
	8	7 4½	23 0
	9	7 7	21 12
Average		6 9½	20 4
Average for all females in survey group		7 7	21 7
Difference between averages with standard error		−13½ oz. ±13½	−19 oz. ±24

Discussion and Conclusions

Nine children have been described in whom the bones of the hands have been remarkably slow to show evidence of ossification. Since the hand is widely used both in the diagnosis of cretinism and as an indication of general skeletal maturity, an apparent anomaly of a normal developmental process must be considered.

Of these children, with the exception of the

TABLE 5

FEEDING AND SOCIAL DATA

Case No.	Feeding						Food Budget		Social Class
	Breast Only until Age:	Supplementary Breast until Age:	Bottle until Age:	Solids at Age:	Difficulties	Vitamins	Expenditure per Adult per Week	Garden	
1	7/52	—	Cows' milk 7/52-7/12	7/12	None	A, C, D	16/–		III
2	5/12	—	—	5/12	None	A, D	12/–	Garden with vegetables	III
3	4/12	5/12	—	4/12	None	A, C, D	35/–		II
4	4½/12	—	Nat. D. milk 4½/12-6/12	4½/12	None	A, C, D	18/–	Allotment with vegetables	III
5	4½/12	9/12	—	4½/12	None	A, C, D	20/–		III
6	5/12	9/12	—	5/12	None	A, C, D	27/–	Garden with vegetables	III
7	5/12	7/12	—	5/12	None	A, C, D	26/–	Garden with vegetables	III
8	4/12	—	Nat. D. milk 4-9/12	5/12	None	C only	27/–	Allotment with vegetables	III
9	—	9/12	Nat. D. milk at night 5/12	5/12	None	A, C, D	22/–		I

cretin (Case 8), only Case 6 can be considered to show more than a fair share of illnesses. It will be remembered that the child had severe physiological jaundice after birth and remained sickly for some months afterwards.

Three of the children, including the premature infant, were light at birth; thus the correlation found for the survey at large between skeletal immaturity and lightness, both at birth and at a year, seems to be substantiated by this small group.

It has been pointed out that although the ossification centres in the knees of these children were slightly retarded, it was in the cretin alone that the marked backwardness visible in the hand was matched by a comparable retardation in the development of the centres of the knee.

Although much work has yet to be done on the value of the hand as an indicator of skeletal maturity, it seems that the following conclusions may be drawn:—(1) Although it has been shown that illness can delay the appearance of osseous centres in the hand of a young child, an immature hand does not necessarily indicate a sick baby. (2) There is a tendency for light children to mature more slowly than heavy ones. (3) Cretinism should not be diagnosed radiographically from the hand alone.

Summary

The histories of nine 1-year-old children with skeletally retarded hands are described. They are selected from 561 children of similar age seen in the Oxford Child Health Survey. Their social background is considered briefly.

One child was diagnosed as a cretin, two were very light at birth (both 5 lb. 1 oz.) and a fourth, a premature child (birth weight 6 lb. 1 oz.), was in hospital for the first month of life because of physiological jaundice.

The correlation found in the entire survey between skeletal maturation and lightness at birth and at 1 year of age seems to be borne out by these nine children.

The conclusion is drawn that although radiographs of the hand alone have great diagnostic worth in cases of skeletal retardation, they are more valuable when considered in conjunction with radiographs of other parts of the skeleton.

I should like to express my gratitude to Dr. Alice Stewart, Director of the Institute of Social Medicine, and to Dr. F. H. Kemp, of the Radcliffe Infirmary, Oxford, for their advice and assistance in the writing of this paper.

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EVIDENCE OF POST-NATAL ENVIRONMENTAL INFLUENCE IN THE AETIOLOGY OF INFANTILE PYLORIC STENOSIS

BY

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The fact that the risk of infantile pyloric stenosis is related to position in family suggests that the environment influences the incidence of the disease, since there is no reason to suppose that inherited differences are affected by birth order, while examples of both pre-natal and post-natal environmental effects associated with birth order are well known (McKeown, MacMahon and Record, 1951a and b). The observation that size of the pyloric tumour is highly correlated with age at operation (McKeown *et al.*, 1951c) supports the view that the tumour develops after birth, but does not, of course, exclude the possibility that the environmental influence (suggested by the association of incidence with birth rank) is exerted before birth. The present communication provides evidence that this environmental effect is post-natal by showing first that immediately after birth the disease is equally common in all birth ranks (it is not until about the third week that the incidence in firstborn is significantly raised), and secondly that symptoms appear earlier in domiciliary than in hospital births.

Risk of Pyloric Stenosis Related to Age and Birth Rank

For all patients (1,059) treated for pyloric stenosis at the Birmingham Children's Hospital in the years 1940-51 we have recorded from case notes the age at onset of symptoms and birth rank. Of these children, 680 were born to Birmingham mothers and 379 to mothers resident outside the city. It should be said at once that 'age at onset of symptoms' is not an entirely satisfactory observation, first because onset is by no means invariably sharp, and may be difficult to identify from the common regurgitation of food by young infants, and secondly, because any such record taken from the mother's statement when the child is admitted to hospital is subject to error. But to have any bearing on the treatment which follows, the errors would have to be selective in respect of birth rank, and we can think of no reason why they should be.

Table 1 shows that the proportions of first, second and third and later births among affected children differ according to their age at the onset of symptoms. The difference is most marked between the first fortnight and the later weeks which are compared in Table 2. Thus the percentage of firstborn among children whose symptoms appeared within two weeks of birth is 43·0, much lower than among children whose symptoms began after the first fortnight (54·4). The difference between these

TABLE 1

PERCENTAGE DISTRIBUTION BY BIRTH RANK ACCORDING TO AGE AT ONSET OF SYMPTOMS*

Birth Rank	Age at Onset of Symptoms (days)							
	0-6	7-13	14-20	21-27	28-34	35-41	42 and over	Total
1	44	42	53	58	53	55	52	52 (540)
2	29	36	29	22	26	28	28	27 (281)
3 and over	27	22	18	20	21	17	20	21 (212)
Total	100 (96)	100 (97)	100 (218)	100 (241)	100 (187)	100 (82)	100 (112)	100 (1,033)

* The table is based on patients treated for pyloric stenosis at the Birmingham Children's Hospital between January, 1940, and October, 1951. In 26 of 1,059 cases records were incomplete.

TABLE 2

PERCENTAGE DISTRIBUTION BY BIRTH RANK OF PATIENTS WITH SYMPTOMS BEFORE OR AFTER THE FOURTEENTH DAY

Birth Rank	Age at Onset of Symptoms (days)	
	0-13	14 and over
1	43·0	54·4
2	32·6	26·0
3 and over	24·4	19·6
Total	100 (193)	100 (840)

$\chi^2 = 8 \cdot 18$, $n = 2$, $0 \cdot 01 < p < 0 \cdot 02$.

* In receipt of a grant from the Medical Research Council.

two percentages (11·4) is significant (standard error ±4·0). This suggests that the relative risk of pyloric stenosis in first births compared with later births is lowest immediately after birth, and increases at about the third week. Indeed, of children whose symptoms appear within the first two weeks of life the proportions in each birth rank (see Table 2) are probably not very different from that of the general population of births from which they are drawn, but to confirm this impression we should require to know the distribution by birth rank of the related population of unaffected births. A rough comparison with an estimate based on the Registrar-General's figures for the region Midland I, 1942-49 (Table 3) suggests that immediately after

TABLE 3

PERCENTAGE DISTRIBUTION BY BIRTH RANK OF PATIENTS WITH SYMPTOMS BEFORE THE FOURTEENTH DAY AND OF ALL LEGITIMATE BIRTHS IN THE REGION MIDLAND I

Birth Rank	Patients with Symptoms within Two Weeks of Birth	Estimated Distribution of All Births in Midland Region I, 1942-49*
1	43·0	41·1
2	32·6	29·1
3 and over	24·4	29·8
Total	100 (193)	100 (745,691)

* Based on the Registrar-General's statistics.
$\chi^2=2·96$, $n=2$, $0·2<p<0·3$.

birth pyloric stenosis may be no more common in first than in later births. Of course we cannot be confident about the validity of a comparison with all births in the region. What is required is the incidence of pyloric stenosis in each birth rank, and this can be given for Birmingham live births notified in the years 1942-49. For this period, from an earlier enquiry (MacMahon, Record and McKeown, 1951), we have fairly reliable estimates of the numbers of Birmingham children (affected and unaffected) in each birth rank, which have been used to calculate the incidence of new cases of pyloric stenosis in first, second and third and later births, according to age at the onset of symptoms (Table 4). The data indicate that there is no definite association between the incidence of pyloric stenosis and birth rank until about the third week of life, and the incidence in firstborn rises sharply in the third and fourth weeks. In Fig. 1 the incidence in each birth rank is shown as a cumulative total.

TABLE 4

INCIDENCE (PER 1,000 RELATED LIVE BIRTHS) OF PYLORIC STENOSIS RELATED TO AGE AND BIRTH RANK*

Birth Rank	Age at Onset of Symptoms (days)							
	0-6	7-13	14-20	21-27	28-34	35 and over	Unknown	Total
1	0·26	0·31	1·00	1·10	0·64	0·72	0·25	4·28 (244)
2	0·24	0·26	0·50	0·52	0·54	0·62	0·10	2·77 (139)
3 and over	0·28	0·14	0·31	0·42	0·26	0·31	0·16	1·88 (95)
Total	0·26	0·24	0·62	0·70	0·48	0·56	0·17	3·03 (478)

* The table is based on Birmingham City cases treated in hospitals during the period 1942-49.

It should be noted that although the incidence in firstborn is undoubtedly raised relative to later births in all subsequent weeks for which the number of cases is large enough to justify examination, from the end of the third week the estimates of incidence may not measure accurately the increased risks to which first births are exposed. The reason is as follows. The incidence of pyloric stenosis is approximately the same in all birth ranks during the first two weeks, and hence it is permissible to regard the raised incidence of onset of the disease in first births in the third week as a reliable measure of increased risk. But the fact that relatively more first births have been affected by the end of the

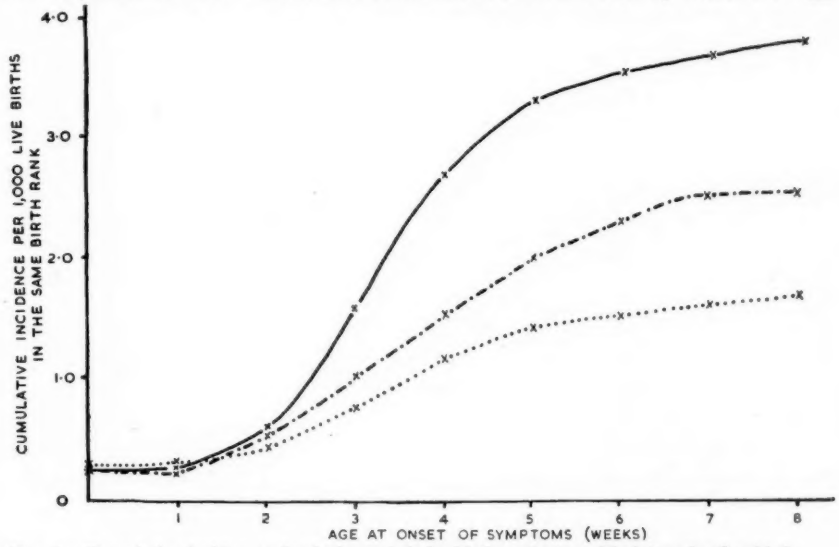

FIG. 1.—Cumulative incidence of pyloric stenosis by birth rank at weekly intervals after birth. The figure is based on Birmingham city cases treated in hospitals during the period 1942-49.
——— = Birth rank 1 ·-·-·-· = Birth rank 2 ····· = Birth rank 3 and over

third week means that fewer susceptible first births remain unaffected at the beginning of the fourth week. (The possibility that some children are more susceptible than others is, of course, entirely compatible with our reservations (McKeown *et al.*, 1951b) about specific inheritance in pyloric stenosis). Hence the incidence of affected among firstborn may somewhat understate the risk compared with the risk to later births in the fourth week. The same considerations apply in all subsequent weeks. This means that the decreased incidence of new cases among first births after the third week cannot confidently be interpreted to mean that the environment is becoming more favourable; in any case it clearly remains unfavourable as compared with the environment of second and later births, and may be relatively more unfavourable than the figures indicate.

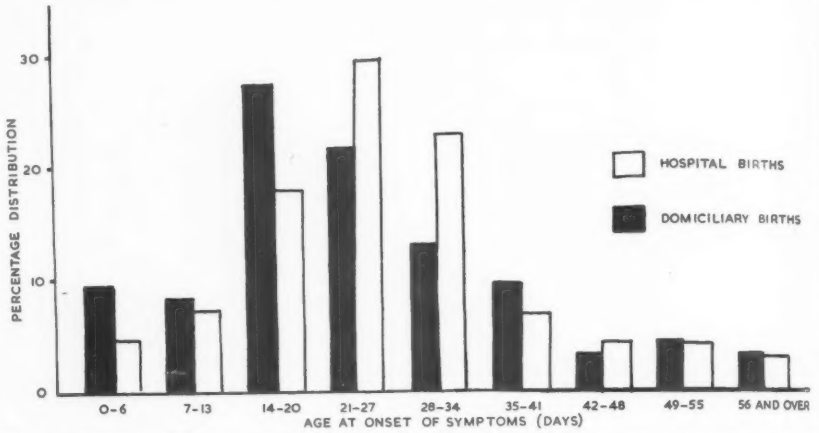

FIG. 2.—Age at onset of symptoms of first-born children with pyloric stenosis born in hospital and at home.

Age at Onset of Symptoms of Children with Pyloric Stenosis Born in Hospital and at Home

The data presented in Tables 1-4 are consistent with the view that the post-natal environment is responsible for the increased risk of pyloric stenosis in first as compared with later births. This environmental influence must be exerted almost immediately after birth, for its effects are evident from the raised incidence of the disease in firstborn in the third week. Since the environment to which children are exposed in the first two weeks of life is related to their place of birth, we now enquire whether there are differences between hospital and domiciliary births (1) in incidence of pyloric stenosis and (2) in age of patients at onset of symptoms.

Unfortunately we cannot give separate figures of incidence for hospital and domiciliary births, because the relative numbers of births at risk are unknown for several of the years under consideration. But in Birmingham a little less than half of all births are delivered in hospital, and in those years which we have examined about half the children with pyloric stenosis were hospital births. We conclude that the incidence of the disease is certainly no lower in hospital than in domiciliary births. Of course, it must be remembered that the proportion of first births, and hence the expected incidence of pyloric stenosis, is higher in hospital deliveries, and a satisfactory comparison cannot be made in the absence of precise figures.

Age at onset of symptoms is, however, quite different in the two cases. The requisite information is given in Table 5 for 782 of the 1,033 cases shown in Table 1 (110 patients were born in nursing homes, and in 141 cases place of birth is unknown). In general, symptoms begin earlier if children are born at home: thus the proportion of patients whose symptoms appeared within three weeks of birth is considerably higher for domiciliary (46·6 %) than for hospital births (31·3%).

It is conceivable that the difference in frequency of onset in the first two weeks might be explained by the fact that mothers whose children are born at home recall the early symptoms more vividly. But the higher incidence in domiciliary births is shown in the third week, by which time children born in hospital have returned to their homes. We have also compared hospital and domiciliary cases in respect of age at operation, since the date of operation is recorded in case notes and is therefore an objective figure. The proportion of patients brought to operation within the first four weeks is 21·2% for domiciliary births, and 15·8% for hospital births (difference $5 \cdot 4 \pm 2 \cdot 9$).

Before concluding that the difference in age at onset of symptoms supports the view that the post-natal environment influences the disease, we must consider the possibility that it merely reflects the well-known difference in parity composition of hospital and domiciliary births, since we have shown that age at onset of symptoms is related to birth rank. In Table 6 (see also Fig. 2) the comparison of age at onset is confined to first births; the results are entirely consistent with those recorded in Table 5 for all births. We conclude that the

TABLE 5

PERCENTAGE DISTRIBUTION BY AGE AT ONSET OF SYMPTOMS OF CHILDREN WITH PYLORIC STENOSIS BORN IN HOSPITAL AND AT HOME

Place of Birth	Age at Onset of Symptoms (days)					
	0-13	14-20	21-27	28-34	35 and over	Total
Hospital ..	14·1	17·2	25·8	24·4	18·5	100 (361)
At home ..	21·9	24·7	22·3	13·8	17·3	100 (421)

$\chi^2=24·3$, n=4, $p<0·01$.

TABLE 6

PERCENTAGE DISTRIBUTION BY AGE AT ONSET OF SYMPTOMS OF FIRST-BORN CHILDREN WITH PYLORIC STENOSIS BORN IN HOSPITAL AND AT HOME

Place of Birth	Age at Onset of Symptoms (days)					
	0-13	14-20	21-27	28-34	35 and over	Total
Hospital ..	11·6	18·2	29·8	23·1	17·3	100 (225)
At home ..	17·8	27·8	21·9	13·0	19·5	100 (169)

$\chi^2=14·3$, n=4, $p<0·01$.

earlier appearance of symptoms in children born at home is attributable to the post-natal environment.

Data from Two Liverpool Hospitals

As a check on the results obtained in Birmingham, we have attempted to record similar information in another city, and we are greatly indebted to the staffs of the Alder Hey and Royal Liverpool Children's Hospitals for giving us access to records of 327 cases. Table 7 gives birth rank in relation to age at onset of symptoms for the 269 patients for whom the data were complete. Numbers are not large enough to give significant results (as in Table 2), but the increase in the proportion of firstborn from the second week is consistent with the trend recorded on Birmingham patients in Table 1. In Liverpool the proportion of births delivered in hospital is considerably higher than in Birmingham, and age at onset of symptoms might therefore be expected to be a little later.

TABLE 7

PERCENTAGE DISTRIBUTION BY BIRTH RANK ACCORDING TO AGE AT ONSET OF SYMPTOMS*

Birth Rank	Age at Onset of Symptoms (days)						
	0-6	7-13	14-20	21-27	28-34	35 and over	Total
1	35	46	44	47	53	42	46 (123)
2	41	42	24	18	25	31	27 (74)
3 and over	24	12	32	35	22	27	27 (72)
Total	100 (17)	100 (24)	100 (54)	100 (51)	100 (59)	100 (64)	100 (269)

* The table is based on patients treated at the Alder Hey Hospital and the Royal Liverpool Children's Hospital in the years 1942-51.

Discussion

For reasons stated elsewhere (McKeown *et al.*, 1951b) and summarized in the opening paragraph of this paper, we regard the increased incidence of pyloric stenosis in first births as evidence of environmental influence in the aetiology of the disease. Our purpose here has been to enquire whether this influence is exerted before or after birth, and we give two reasons for believing it to be post-natal. (1) The disease is about equally common in all birth ranks until the third week of life. (2) The onset of symptoms is earlier in domiciliary than in hospital births.

It may be objected that manifestation of a pre-natal environmental influence might conceivably be delayed until a few weeks after birth. This explanation would be more impressive if the influence were manifested on the earliest cases. Moreover, it would not account for the difference in age at onset of symptoms between domiciliary and hospital births which can hardly be explained otherwise than as a post-natal environmental effect.

If these views are correct it is of considerable practical importance to consider the nature of the environmental influence, upon which the possibility of future control of the disease may depend. At present we have no direct evidence, but the data suggest that the unfavourable environment exerts its effect almost from birth on patients born at home, and after their return home on patients born in hospital.

Finally, the fact that the incidence of cases which arise in the first two weeks of life is unrelated to birth rank suggests that they are different aetiologically from later cases. For 79 patients whose symptoms appeared within two weeks of birth we have therefore examined (*a*) the incidence of pyloric stenosis in sibs, (*b*) the incidence of pyloric stenosis in cousins and (*c*) the incidence of consanguinity of parents. Numbers are, of course, small, but the results are the same as those obtained when all patients were considered (McKeown *et al.*, 1951b); that is to say we have no evidence of specific inheritance in the early cases.

Summary

Evidence of post-natal environmental influence in the aetiology of pyloric stenosis is provided by an investigation of 1,059 patients treated at the Birmingham Children's Hospital in the years 1940-51.

Immediately after birth the disease is equally common in all birth ranks, but the incidence in first births rises sharply in the third and fourth weeks

and remains raised relative to later births in all subsequent weeks examined. The percentage of firstborn among children whose symptoms appeared within two weeks of birth was 43·0, much lower than among children whose symptoms began after the first fortnight (54·4).

The onset of symptoms is earlier in domiciliary than in hospital births. Thus, symptoms appeared within three weeks of birth in 46·6% of children born at home, and in 31·3% of children born in hospital. This difference is not explained by differences in parity composition of hospital and domiciliary births, and is even greater when first births are considered separately.

We are indebted to Professor J. M. Smellie and the staff of the Birmingham Children's Hospital, and to Professor N. B. Capon and the staffs of the Alder Hey and Royal Liverpool Children's Hospitals, for permission to use their records and for the facilities made available to us.

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TWO CASES OF HAND-SCHÜLLER-CHRISTIAN DISEASE IN INFANCY

BY

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The diversity of the clinical features of Hand-Schüller-Christian disease is well recognized. Although it is a disorder affecting chiefly young children, its occurrence in the first year of life is rare.

The two cases presented here indicate that the form of the disease found in infants tends to be more rapid in its course and the lesions more widespread than in older children. At the same time they appear clinically and in certain pathological respects to occupy a position intermediate between the more common varieties of Hand-Schüller-Christian disease and the non-lipoid reticuloendotheliosis of infants known as Letterer-Siwe disease. It is considered that this report provides further evidence in support of the view that these two conditions are closely related, particularly on clinical grounds, although some pathological evidence is brought forward to suggest that there may be good reason to separate Letterer-Siwe disease and the acute variety of Hand-Schüller-Christian disease on the basis of histology.

Case Reports

Case 1. Shirley T. was admitted to The London Hospital on October 25, 1944, at the age of 9 months. Her parents and an elder brother and sister were quite well, and the pregnancy and labour had been normal. There was some difficulty with feeding until the age of 6 weeks when breast feeding was replaced by a cow's milk mixture. At the age of 3 weeks her mother noticed that there were three red spots on the roof of the mouth. The significance of this observation is not known and no further mention of it is made in the case notes.

At the age of 4 months (five months before admission) the right side of the face became swollen. At first the child was thought to be suffering from mumps but shortly afterwards she was admitted to a hospital near her home, and the cervical lymph nodes were incised. The only material obtained at the operation was said to be congealed blood. The lymph nodes on both sides of the neck increased in size and the child's general condition deteriorated rapidly.

On admission she was extremely ill, pale, dyspnoeic and cyanosed. The temperature was 96° F., the pulse 154 per minute and respirations 86 per minute. Large subcutaneous masses were found on both sides of the neck. They were firm, smooth, and fixed to the deep structures. The percussion note at both posterior lung bases was impaired and coarse crepitations were heard in all areas. The abdomen was very distended, the liver just palpable, and the spleen was firm and enlarged to three fingersbreadths (2 in.) below the costal margin. There was no evidence of free fluid. Other systems were normal.

The urine was normal.

Examination of the blood showed: haemoglobin, 63% (9·3 g.%); red blood cells, 3,300,000 per c.mm.; colour index, 0·95; leucocytes, 15,850 per c.mm. (neutrophils 60%, eosinophils 2%, lymphocytes 36%, monocytes 2% and 1 normoblast in counting 200 white cells).

A radiograph of the chest showed numerous soft opacities scattered throughout both lung fields presenting a 'snow storm' appearance. There was also a large mass occupying the superior mediastinum.

Radiographs of the skull and spine revealed defects in the frontal, parietal and occipital bones, and collapse of the body of the ninth dorsal vertebra. (It is regretted that the original x-ray films of the patient have been mislaid, so that their reproduction is not possible.)

The child was nursed in an oxygen tent and her condition improved slightly. There was some pyrexia (100°-101° F.) which became more marked shortly before death. She received two treatments with deep x-rays to the lung fields, and immediately after the second she became extremely dyspnoeic and died suddenly seven days after admission.

Pathological Findings

The following is a summary of necropsy (P.M. 223/44) performed 20 hours after death: bronchopneumonia, severe emphysema and Hand-Schüller-Christian disease, with infiltration of the thymus, lungs, liver, lymph nodes and bones.

Macroscopic Appearances. The following were noted.

THYMUS. The gland was of normal shape, rubbery and flexible with, on section, a coarse reticulum of pink and grey fibrous areas separating areas of a bright yellow, lipoidal appearance.

FAUCIAL AND PHARYNGEAL TONSILS. These were normal.

LYMPH NODES. The occipital and cervical groups were enlarged (up to 3·5×2·5 cm.) with soft, swollen and purple cut surfaces showing a few pale, yellowish grey areas. The gastro-coronary and coeliac groups were slightly enlarged with pale, grey, yellow-flecked cut surfaces. The bronchial, axillary and mesenteric groups appeared normal.

SPLEEN. The spleen was slightly enlarged (21·3 g.) with a normal cut surface.

LIVER. The liver weighed 226·8 g., and numerous rounded and stellate grey fibrous nodules (up to 1·0 cm. diameter), sparsely speckled with yellow, were scattered throughout the cut surfaces.

LUNGS. Both were beset everywhere with cysts (up to 0·9 cm. diameter) often separated by fibrous strands. Confluent nodules resembling organizing bronchopneumonia were present in both lower lobes and in the posterior parts of both upper lobes.

BONES. Both occipital and parietal bones presented foci of bone destruction (from 0·5 cm. diameter to 2·5 cm. diameter) filled with soft purple and orange rusty tissue not projecting above the bony surfaces. Replacement of the sella turcica by similar tissue made it difficult to remove the pituitary gland. The body of the ninth dorsal vertebra was completely collapsed and showed a subpleural projection of soft grey tissue overlying it on the right side. Small, faint grey areas of bone destruction were visible in other vertebral bodies. There was a pathological fracture in the middle of the ninth left rib covered by a subperiosteal mass of soft grey tissue. The remaining ribs were normal. Red marrow occupied the medullary cavities of the right femur, tibia and fibula, the sternum, the clavicles and the right side of the pelvis. The other bones were not examined.

KIDNEYS. The kidneys weighed 42·5 g. and moderate parenchymatous degeneration was noted.

No abnormality was demonstrated in the heart (28·35 g.), gastro-intestinal tract, thyroid (0·9 g.), suprarenal glands (2·85 g.), genital tract and brain (772·2 g.). The middle ears were clean.

The body (5·2 kg.) was considerably wasted and the eyes deeply sunken. No skin lesions were found.

Microscopical Examination. All paraffin sections were stained with Ehrlich's haematoxylin and eosin, Van Gieson's stain and Weigert's elastic stain. Where necessary sections were prepared by Laidlaw's and by Foot's methods for reticulin, and by Perl's method for iron. Frozen sections were stained for fat with Sudan III, for phospholipins by the Smith-Dietrich method, and for cholesterol esters by the Schultz method. Weil-Davenport silver impregnation (Marshall's modification, 1948) was done on selected blocks.

THE THYMUS. The thymus exhibited the fullest development of the lesion, and indeed no normal thymic tissue could be identified. The gland was completely replaced by collections of cells with irregular polygonal and spindle-shaped outlines and a lightly eosinophil faintly granular cytoplasm. Their nuclei were for the most part pale and vesicular with fine chromatin strands; they were oval or twisted and indented, and showed no nucleoli. Other rather larger cells were moderately numerous and these possessed one or two distinct nucleoli and more densely staining chromatic network. Also present were rounded multinucleate giant cells, with 12 to 15 nuclei often arranged in rosette fashion and occasionally with nuclear debris in their cytoplasms (Fig. 1). These cellular collections were broken up by slender bundles of collagen fibres; scanty cords of lymphocytes and a few eosinophil leucocytes were scattered irregularly throughout. Foam cells were numerous in many areas especially in relation to the collagen bundles (Fig. 2), and many giant cells also showed vacuolation of their cytoplasm. These cells were shown to contain abundant sudanophil lipoid while other cells contained only a few cytoplasmic droplets or none at all. The polarizing microscope demonstrated in the foam cell areas abundant doubly refractile lipoid which, on heating the slide gently and allowing it to cool, reappeared as 'Maltese crosses'; the Schultz reaction was strongly positive, and the Smith-Dietrich test for phospholipins was abundantly positive in most vacuolated cells. With the Weil-Davenport impregnation method these mononuclear cells resembled macrophages in their strongly argyrophilic reaction and irregular cytoplasmic processes (Fig. 3); considerably enlarged and bizarre forms were numerous. The multinucleate giant cells and the rounded foam cells were also argyrophilic. Reticulin impregnations demonstrated many reticulin fibrils in relation to the collagen strands and around capillaries, but only a few delicate fibrils in the cellular areas.

LUNGS. In the lungs mononuclear cells similar to those in the thymus extensively infiltrated the alveolar walls, and formed nodular masses in which the reticulin framework of the alveoli could still be clearly traced. There was only a slight increase in reticulin fibrils in the infiltrated areas, and scanty fibrosis. Eosinophils and lymphocytes were scanty, while neutrophil leucocytes were in moderate abundance in the alveoli and alveolar walls, presumably the result of the terminal respiratory infection. Multinucleate giant cells were not numerous, and lipoid was present only in scanty quantities. Many alveoli were enormously dilated and there was considerable widening of infundibular spaces and of terminal bronchioles. While the appearances suggest that this process of dilatation was probably responsible for the larger cysts, the detailed study required to eliminate other alternatives is beyond the scope of the present article.

LIVER. In the liver similar nodular infiltration was found in the portal systems, and foam cells with sudanophil lipoid were abundant in the larger masses. Multinucleate giant cells were few and eosinophils were not seen.

LYMPH NODES. Sections of lymph nodes sampled from axillary, upper cervical, gastro-coronary, coeliac and occipital groups all showed the same general picture of complete replacement of lymphoid tissue by mononuclear cells similar to those in the thymus and elsewhere. The capsules of the nodes were everywhere intact. The subcapsular sinuses were dilated and filled

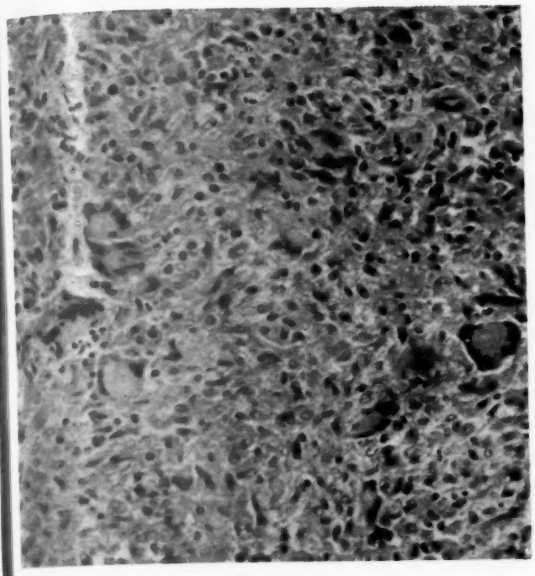


FIG. 1.

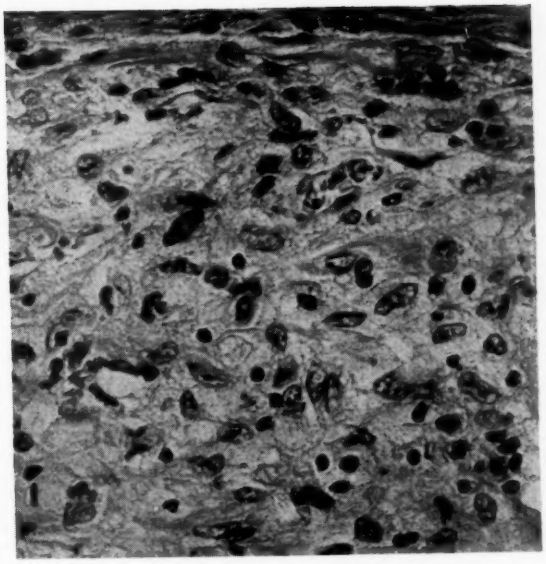


FIG. 2.

FIG. 3.

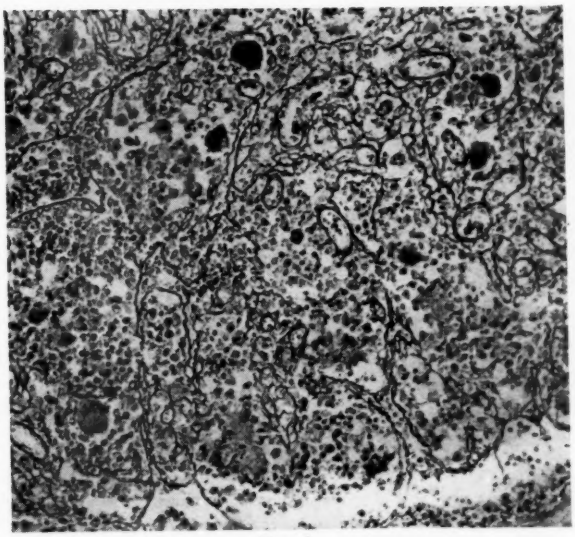


FIG. 4

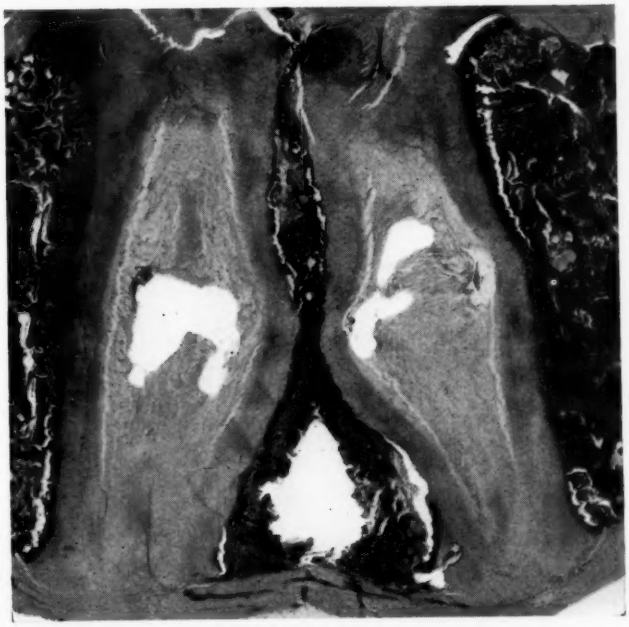


FIG. 5

IG. 1.—Thymus in Case 1: closely packed non-foamy mononuclear cells and giant cells. Van Gieson's stain (×175).

IG. 2.—Thymus in Case 1: foam cells beside a band of collagen. Van Gieson's stain (×390).

G. 3.—Thymus in Case 1: argyrophilic cells from an area not containing lipoid. Weil-Davenport silver impregnation (×325).

G. 4.—Lymph node in Case 1: reticulin impregnation (Foot's ethod). Giant cells are conspicuous and are darkened by the ver. In the bottom right hand corner is the subcapsular sinus (×110).

G. 5.—Collapsed body of ninth thoracic vertebrae between adjacent intervertebral discs in Case 1. Haematoxylin and eosin (×7).

with proliferating mononuclear cells. The demarcations between the pulp and the remaining sinuses were lost and only a very occasional ill-defined ring of small lymphocytes remained to indicate the site of the lymphoid follicles. Reticulin fibrils were not increased (Fig. 4). Giant cells were moderately numerous and foam cells, though present in scanty groups in the upper cervical gland, were not found elsewhere. The fat in the upper cervical gland had the same characters as that in the thymus. Eosinophil leucocytes were variable in numbers but were never abundant, and neutrophils were similarly distributed among the proliferating cells. Small haemorrhages were common and a scanty amount of iron pigment was associated with erythrophagocytosis by the mononuclear cells.

SPLEEN AND THYROID GLAND. The spleen contained only one minute focus of proliferating mononuclear cells in relation to the adventitia of a small arteriole. A small focus was also present in the thyroid gland between the acini. In the dural capsule surrounding the pituitary gland there were numerous foam cells and mononuclear cells with scanty eosinophil leucocytes, but the gland itself was not invaded.

THE BONES. Sections from the vault and base of the skull, from the left ninth rib, from the bodies of the eighth to the tenth thoracic vertebrae, from the head of the femur and of femoral marrow were examined. Except for the head of the femur, which appeared normal, all bone sections showed more or less extensive areas of mononuclear cell proliferation in the medullary spaces associated with bone destruction. This was especially marked in the body of the ninth thoracic vertebra (Fig. 5) where the space between the two intervertebral discs was occupied by a few partly necrotic bone fragments among a small number of proliferating cells. The marrow of the eighth and tenth thoracic bodies was extensively infiltrated and foam cells and giant cells were numerous. In the ninth left rib, which showed a pathological fracture, there was a little callus formation beneath the periosteum at one point over the fracture. Some fibrosis was present here but was not conspicuous in any of the other bone lesions. Eosinophils were not numerous in any bone lesion, though they were present in all, usually in association with an equal number of neutrophil leucocytes and a few small lymphocytes.

Sections from cerebral cortex, the floor of the third ventricle through the pituitary stalk, basal ganglia and hind-brain showed no histological abnormality. No abnormal changes were found in sections of either suprarenal glands, the posterior third of the tongue or of the oesophagus.

Case 2. Susan M., aged 1 year and 2 months, was admitted to The London Hospital on July 4, 1950. She was the only child of healthy parents and had been born six weeks before term after an otherwise normal pregnancy. Birth weight was 5 lb. 12 oz. The child was breast fed for two weeks only and the feeds were then changed to a dried cow's milk mixture.

At the age of 1 month the mother noticed a skin eruption which appeared in both groins. This was at first erythematous and later scaly in appearance. It appeared to irritate the child considerably at times, particularly at night and during periods of teething. At the age of 8 months a dermatologist had been consulted and a diagnosis of infantile eczema was made. Local applications produced only temporary improvement and the eruption gradually spread to involve the trunk, limbs and, more recently, the scalp. At no time had the face been affected.

At the age of 8 months (six months before admission) slight prominence and frequent watering of the right eye was noted. This had not worried the parents unduly, and it was not until a few weeks before she came into the hospital that the proptosis became more obvious. At this time a large mass was first noticed in the right side of the neck, and this rapidly increased in size. The child became fretful, looked pale, began to lose weight and excessive thirst was noted by the parents.

On admission the patient appeared extremely ill. She was very fretful, pale and moderately wasted. Her weight was 16 lb. 4 oz., the temperature 101° F., pulse 152 and respirations 34. The face was asymmetrical and there was also a moderate degree of plagiocephaly. Both eyes were prominent, the right showing obvious proptosis, and in the right temporal region there was a soft, smooth, fluctuant swelling extending backwards from the lateral angle of the orbit as far as the ear. Pressure on this swelling caused further protrusion of the right eye, and deep palpation revealed a defect in the underlying skull and lateral wall of the orbit.

The skin of the trunk and proximal parts of the limbs was covered by a diffuse scaly eruption, most marked in the groins and axillae (Fig. 6). The scales were dry and brownish-red, although in some places they were separated by moist weeping areas. There were a few similar lesions on the scalp, but no part of the skin of the forehead and face was affected. There was no purpuric element in the eruption.

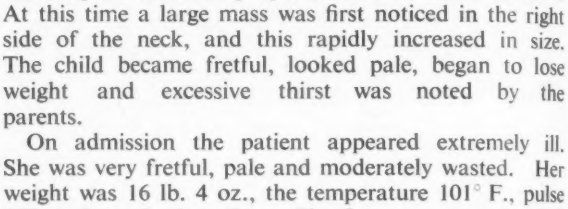


FIG. 6.—Photograph of Case 2 showing the scaling rash.

Both ears showed severe otitis externa, and a reddish polypoid mass was attached to the anterior wall of the right external meatus.

The lymph nodes in both groins and axillae were moderately large and discrete, and in the neck there was considerable enlargement of the tonsillar groups on the right side.

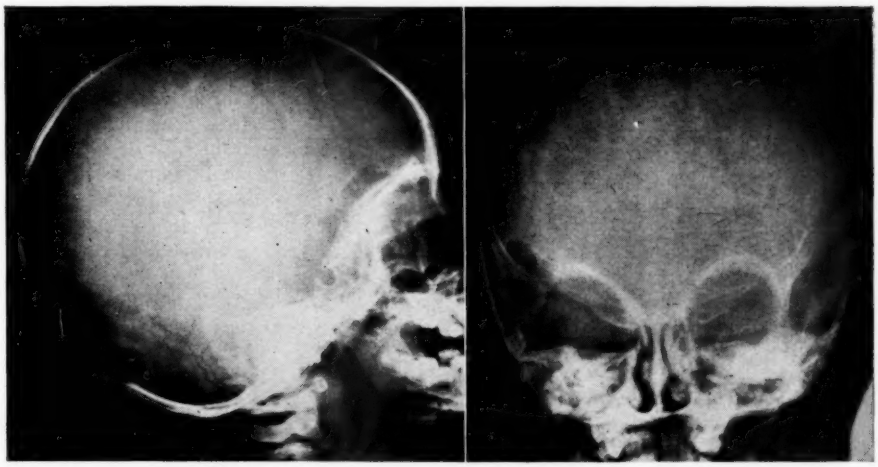
The abdomen was distended and a large smooth liver could be felt two inches below the costal margin. There

was no palpable enlargement of the spleen, and no evidence of ascites.

The respiratory, central nervous and cardiovascular systems appeared quite normal.

The urine was turbid and a cloud of albumin was present; the deposit showed a considerable excess of pus cells. Culture produced a growth of *Bact. coli*, faecal streptococci and *Proteus*.

Blood examination showed: haemoglobin, 47% (7·0 g.%); leucocytes, 17,000 per c.mm. (neutrophils 67%, lymphocytes 32%, monocytes 1%). There was slight anisocytosis and polychromasia of red cells. The platelets were plentiful.



7a 7b

FIG. 7.—Frontal and lateral radiographs of skull of Case 2 showing the sharply defined bony defect in the right temporal region.

Radiographs of the skull (Figs. 7a and b) revealed a large area of bone destruction on the right side involving the squamous portion of the temporal bone, and also the posterior and lateral walls of the orbit. Radiographs of the long bones taken after death did not show any further bony defects.

A clinical diagnosis of Hand-Schüller-Christian disease was made, with neuroblastoma of the suprarenal as a likely alternative.

In view of the child's poor general condition and the extent of the lesions the prognosis was considered hopeless, and the treatment was restricted to symptomatic measures. Soon after admission the patient developed signs of bronchopneumonia and she died on the fifth day.

Pathological Findings

Necropsy (P.M. 253/50) was performed 17 hours after death. The results showed respiratory failure, and Hand-Schüller-Christian disease with infiltration of the thymus, spleen, liver, lymph nodes, lungs and skull bones.

Macroscopic Appearances. The following were noted.

THYMUS. The gland was slightly shrunken and replaced by nodular opaque bright yellow and grey-white rubbery tissue with occasional softer grey areas.

LYMPH NODES. These were generally enlarged with soft purple and grey cut surfaces flecked with petechial haemorrhages. The upper cervical groups were largest (measuring up to 3·5 × 2·5 × 2 cm.) and showed opaque yellow flecks on section. The paracolic, iliac and lumbar groups were less conspicuously enlarged.

SPLEEN. The spleen (21·3 g.) was rather firm, slightly enlarged, with on the cut surface, conspicuous Malpighian bodies and ill-defined grey areas (up to 0·4 cm. diameter), in the pulp.

LIVER. The liver (382·7 g.) was fatty and buff coloured.

LUNGS. The lungs were poorly aerated and, on section, the surfaces were studded with numerous grey and yellow nodules (up to 3·5 cm. diameter) showing occasional small cysts at their peripheries.

SKULL. The skull was asymmetrical, the right half being skewed anteriorly, due to a mass of mahogany-brown and grey tissue mottled with yellow which both infiltrated the right temporalis muscle and fascia and occupied a bony defect (3 cm. diameter) in the right squamous temporal bone and the adjacent lateral orbital wall. The orbital contents were unaltered. Similar yellow and grey infiltration involved the lateral aspects of the pituitary fossa spreading into the cavernous sinuses, and there was a band of infiltrating tissue in the basisphenoid beneath the sella turcica. The middle ears contained grey exudate flecked with yellow. Tissue of the same nature also infiltrated the dura around the torcular herophili, but the skull here was intact.

SKIN. A diffuse, silvery-brown scaling rash, in parts hyperkeratotic, in parts with shallow ulceration, covered the entire front and back of the trunk, most marked over the abdomen and the chest, reaching from the occiput and shoulders to the axillae and down to the groins. The skin of the arms, legs and face was clear, except for a punctate rash on the palms and soles.

The right femur and humerus, the sternum, the heart (49·6 g.), the gastro-intestinal tract, the thyroid (1·25 g.), the suprarenal glands (6·5 g.), the kidneys (77·2 g.), and the genito-urinary tract showed no abnormality.

The body weighed 6·55 kg.

Microscopical Examination. Paraffin sections were prepared as in Case 1.

LYMPH NODES. The normal architecture of all nodes examined was almost entirely replaced by sheets and ill-defined nodules of actively proliferating irregular plump cells with eosinophil, faintly granular cytoplasm, and pale staining oval, often twisted, nuclei. Nucleoli were not visible in the majority, but a few larger cells with conspicuous nucleoli were seen. Many binucleate, and a moderate number of multinucleate giant cells were present. The capsules were everywhere intact, though a few mononuclear cells were occasionally found

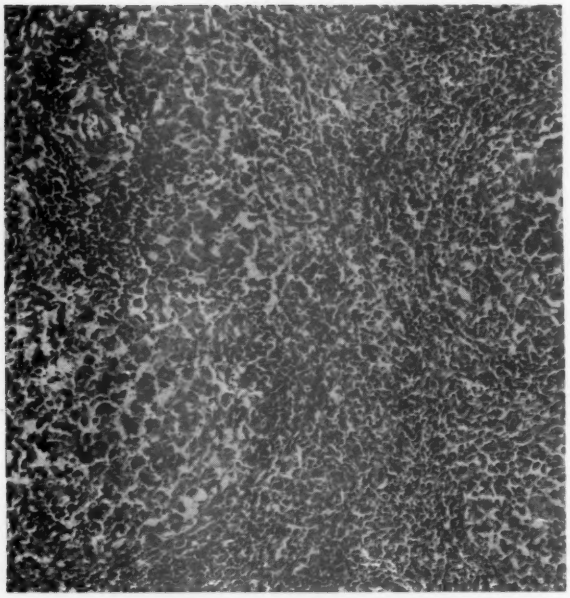


FIG. 8.—Spleen of Case 2: sharply circumscribed nodules of histiocytes in the pulp. Haematoxylin and eosin (×110).

in the perinodal connective tissues. In one of the right upper cervical nodes narrow compressed strands of small lymphocytes formed broken rings in the expected position of the lymphoid follicles, suggesting that proliferation of mononuclear cells had occurred within the follicles as well as in the medullary pulp. The subcapsular sinuses were filled with cells, but elsewhere the pattern of sinuses and medullary cords was lost. There was no increase in reticulin fibrils, and no fibrosis. A few foam cells were found in the right upper cervical node but in none of the others. Eosinophils were scanty and in equal numbers with neutrophil leucocytes. Small haemorrhages had occurred regularly in many nodes, and the mononuclear cells around these were actively phagocytic of red cells while some contained a little iron pigment. Occasional small foci of necrosis were seen in the nodular collections of cells.

SPLEEN. Discrete nodules of mononuclear cells were scattered closely throughout the section (Fig. 8); they were not related to the Malpighian bodies which were atrophic and consisted of small lymphocytes only. Microscopic haemorrhages were present in several of the nodules and erythrophagocytosis and a little iron pigment were seen in the adjacent cells. There were no foam cells. Eosinophils were scanty. There was a slight increase in reticulin fibrils around the nodules but none within them. With the Weil-Davenport method most of the mononuclear cells were strongly argyrophilic and showed plump cell bodies with irregular processes. A similar result was obtained with silver preparations from lymph nodes.

THYMUS. The gland was completely replaced by a network of coarse bundles of collagen fibres and spindle fibroblasts, within the interstices of which were numerous closely packed mononuclear cells similar to those elsewhere. Foam cells were numerous, especially adjacent to the collagen bundles, but not in the centres of the cellular areas. No eosinophils were seen, though small lymphocytes were present in scanty groups.

LIVER. There was a similar infiltration in many portal tracts unaccompanied by foam cells, fibrosis or eosinophils.

LUNGS. Nodules of mononuclear cells with abundant associated reticulin fibrils and numerous foam cells destroyed the alveolar architecture over large areas. Collagen fibres were abundant focally in the nodules, but eosinophils were very scanty. Considerable dilatation of many alveolar spaces, infundibula and terminal bronchioles was found in the neighbourhood of these nodules.

PITUITARY GLAND. The capsule of the gland was heavily infiltrated with cells amongst which foam cells were numerous, but the gland itself was intact. A similar infiltration was present in the dura from the torcular herophili.

SKULL BONES. The basisphenoid, the right lesser wing of the sphenoid, and the right middle fossa showed extensive destruction of bone with replacement by infiltrating tissue with numerous foam cells and multinucleate giant cells, but both eosinophils and fibrosis were inconspicuous, the last mainly covering the surfaces of the cellular masses.

SKIN. The superficial layers of the corium were occupied by irregular, non-foamy, mononuclear cells and focal ulceration of the overlying epidermis was seen (Fig. 9).

Sections of the thyroid gland, the suprarenal glands and the posterior mitral cusp did not reveal any abnormality. Careful examination of the brain sections taken from the floor of the third ventricle, both caudate nuclei, and occipital and parietal regions of the brain after some weeks' hardening in formalin showed no histological abnormality.

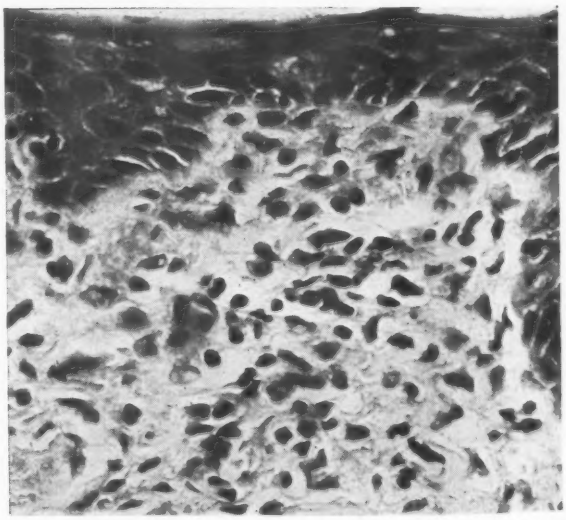


FIG. 9.—Skin of abdomen in Case 2 showing proliferating histiocytes in the subepidermal layer. Haematoxylin and eosin (×425).

Lipoid Studies on Case 2. Frozen sections from blocks of tissue fixed in formol-calcium were examined with Sudan III and Sudan black B. Plentiful sudanophilic lipoid droplets were seen in the foam-cell areas of the thymus, and sections from the same regions, stained with Nile blue sulphate, showed a moderate amount of purple-staining material indicating the presence of neutral fats; examination with the polarizing microscope revealed abundant anisotropic lipoid, which disappeared on gentle heating and reappeared on cooling as ' Maltese crosses '; the Schultz reaction was strongly positive and digitonide crystals formed in large numbers. It was concluded from these findings that a mixture of neutral fats, cholesterol and cholesterol esters was present. The Smith-Dietrich stain and Baker's (1946) acid haematin-pyridine procedure for phospholipins both showed a considerable amount of indigo-blue staining lipoid material in the foam-cell areas, but in view of Lison's (1936) warning concerning the interpretation of the Smith-Dietrich stain in the presence of cholesterol and its esters, no definite conclusion as to the presence of phospholipins in the lipoid mixture could be reached.

A similar mixture of fatty substances was found in the lesions in the lungs and in the mass from the right lesser wing of the sphenoid, but only scanty quantities of sudanophil and anisotropic fat were detected in one coeliac and one right upper cervical lymph node. No lipoid substances were found in the spleen, the portal infiltration in the liver or in the skin lesions. The above qualitative results appear to agree with quantitative lipoid studies, quoted by Thannhauser (1950b) on lesions in Hand-Schüller-Christian disease.

Discussion

Hand-Schüller-Christian disease is usually recognized as a chronic disorder chiefly affecting children and adolescents, of which the pathological basis is a multifocal proliferation of histiocytes associated with the presence of lipoid, predominantly cholesterol and its esters. In addition, eosinophils are usually conspicuous in the lesions. The classical triad of diabetes insipidus, exophthalmos and bone deposits is by no means a constant finding, for the clinical picture is extremely variable and depends largely on the situations involved in the disease process. The bones are especially affected, and involvement of the viscera is not uncommon.

The majority of cases occur under the age of 12 years, and the maximum incidence is in the second, third and fourth years of life (Dauksys, 1935). Onset of the disease in the first year of life is unusual.

A disease peculiar to infants and young children which is characterized pathologically by histiocyte proliferation, but no lipoid-containing foam cells in the affected tissues, has been called Letterer-Siwe disease by Abt and Denenholz (1936). Siwe (1933, 1949) describes the condition as a disease of unknown aetiology with an acute or subacute onset, fever, progressive anaemia, purpuric skin rashes, hepato-splenomegaly and localized bone defects. These last may not be detected clinically but, according to the author, are always present histologically. The outcome is invariably fatal after an illness which may last for several months. Siwe emphasizes that cells containing fat are not prominent in the lesions and lipoid-containing foam cells are not to be found. There are about 30 reports of the disease in the world literature but examples in the British literature are very few, the first being the cases recorded by Gittins (1933) and the most recent that of Claireaux and Lewis (1950). The latter paper reviews the condition and summarizes current views concerning the relationship between Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma of bone. The last term is applied to a solitary destructive lesion in bone, occurring chiefly in children and young adults, which is regarded by most authors as a unifocal manifestation of Hand-Schüller-Christian disease. Spontaneous healing by resolution (Jaffe and Lichtenstein, 1944) or by fibrosis with or without lipidization (Green and Farber, 1942) is the common result.

The evidence in favour of the essential unity of these conditions has been steadily accumulating. Glanzmann (1940) remarked upon the resemblance between the bone lesions in Hand-Schüller-Christian disease and Letterer-Siwe disease, and the similarity of the basic pathology has been reviewed by Wallgren (1940), Jaffe and Lichtenstein (1944) and others. Following these publications attention has been drawn to cases with transitional features which appear to link up the two conditions; for example, Wallgren's (1940) two cases and the report of Flori and Parenti (1937).

Our primary concern in reporting these two cases is to indicate their relationship to the acute form of reticulosis in infants (Letterer-Siwe disease) and also to the more chronic disease found as a rule in older children (Hand-Schüller-Christian disease).

In both children the disease began in early infancy. In Case 1 the lesions in the roof of the mouth were probably not significant and, after initial feeding difficulties, the child progressed normally until the age of 4 months, when enlargement of the cervical lymph nodes was first observed. She died, five months later, after a steadily progressive course. Case 2 is particularly interesting in that skin lesions appeared at the age of 1 month, and this was undoubtedly the first manifestation of the disease. A period of just over one year elapsed from the onset of symptoms until death. In respect of duration of the illness and their age,

therefore, these two children resemble many other reported cases of Letterer-Siwe disease. Further resemblances to this condition were found in the appearance of fever, anaemia, enlarged lymph nodes, hepato-splenomegaly and bone defects (multiple in the first and confined to the skull in the second case). They differ from the accepted clinical concept of Letterer-Siwe disease, however, and resemble Hand-Schüller-Christian disease by the presence of radiological evidence of pulmonary involvement in the first case, and of exophthalmos and an extensive skin eruption in the second case. In fact, Case 1 was included in a series of cases in a paper on 'honeycomb lungs' by Oswald and Parkinson (1949, Case 1) in which they discussed similar changes in other reported cases of Hand-Schüller-Christian disease.

Siwe (1949) has stressed the frequent occurrence of petechial skin lesions as part of the disease described by him, although some of the cases accepted as examples of Letterer-Siwe disease have not shown this feature. Furthermore, petechia-like lesions are not rare in cases of Hand-Schüller-Christian disease (Thannhauser, 1950a). Reye (1948) records the appearance of a petechial skin rash in a case of Letterer-Siwe disease eight months before death and, although he does not mention the clinical progress of the skin lesions, the post-mortem description of the rash and the histological appearances closely resemble those of our second case. So far as is known there was no clinical evidence of skin involvement in our first case and none was found at necropsy; there was certainly no petechial element in the scaly eruption of Case 2. This is of considerable interest, for the child presented with a flexural eruption and, although the lesions progressed to affect the trunk and scalp, there was never any involvement of the face such as is usually seen in cases of infantile eczema. A similar affection of the skin with the same distribution and reddish-brown scaly appearance is known to occur in cases of Hand-Schüller-Christian disease (Merritt and Paige, 1933; Lane and Smith, 1939; Curtis and Cawley, 1947), but has not, so far as we know, been reported in cases of Letterer-Siwe disease other than in the one described by Reye.

At necropsy there was a remarkable similarity between our two cases. Both showed widespread visceral changes and focally destructive bone lesions. Conspicuous in both were deposits of yellow lipoid material most noticeable in the thymus, the lungs and the bone lesions. Although macroscopically the disease appeared without doubt to be in each case Hand-Schüller-Christian disease, on microscopical examination several features deviated from the descriptions of that disease by Fraser (1935) and Englebreth-Holm, Teilum and Christensen (1944) in such ways as at first to cast some doubt on the diagnosis. According to these authors the mature lesions of Hand-Schüller-Christian disease consist of a proliferation of histiocytes with numerous fat-laden foam cells, eosinophil leucocytes and a variable number of collagen fibres. It has been seen that eosinophils were not a conspicuous feature in any part of these two cases, and fibrosis and foam cells were only focal features in the thymus and lung lesions, while in the lymph nodes the changes consisted largely of proliferating histiocytes, and foam cells were very rarely found. It was in this last site in both cases, and in the spleen in Case 2, that the changes were most reminiscent of Letterer-Siwe disease. In this condition there is a widespread histiocytic proliferation in viscera and bones unaccompanied by fat accumulation, while most authors make little mention of the presence of eosinophil leucocytes, and fibrosis is not seen. The absence of lipoid in the lesions is one of the cardinal points in the arguments of Abt and Denenholz and of Siwe himself for separating this condition sharply from Hand-Schüller-Christian disease. Their arguments are, however, considerably weakened by the report of a case by Flori and Parenti (1937) of an infant in whom a lymph node biopsy performed 10 months before death showed a non-lipoid reticulo-endothelial hyperplasia, while at necropsy widespread lipoid deposits and fibrosis were found in many organs, including the thymus gland. Again eosinophils were inconspicuous in their case, and in this as well as in most other features the changes were closely similar to those in our two cases. Flori and Parenti regarded their case, on clinical as well as pathological grounds, as one of Hand-Schüller-Christian disease and it has been accepted as transitional between this condition and Letterer-Siwe disease by most authors. Siwe on the other hand regarded this case as atypical Hand-Schüller-Christian disease and not related to the condition bearing his name because of the lipoid accumulations. Wallgren, however, pointed out that lipoid deposits and fibrosis could be related to the chronicity of the condition and were not primary features in the disease process. Further, Fraser (1935), and Englebreth-Holm, Teilum and Christensen (1944), showed that the earliest phase of Hand-Schüller-Christian disease was a pure proliferation of histiocytes while the other features of the histology emerged in various stages subsequently. Attention has been paid in this study to the presence or absence of eosinophil

leucocytes in both cases, the relative paucity of which contrasts with the descriptions of Hand-Schüller-Christian disease by the authors mentioned. The rôle of eosinophil leucocytes in tissue reactions is uncertain and it is difficult at this stage to attach much significance to their scarcity here, but attention is drawn to a case reported by Jaffe and Lichtenstein (1944) of a 10-month-old girl with a typical eosinophilic granuloma of bone on which a biopsy was performed. The infant died after a short illness and at necropsy the lesions were described by the authors as those of Letterer-Siwe disease; they also noted the curious absence of eosinophil leucocytes, so prominent in the biopsy specimen. Whatever their rôle, it is undoubtedly a secondary one in the disease process, and variations in their number must not be allowed to obscure the essential abnormality of histiocytic hyperplasia fundamental in the pathology of Hand-Schüller-Christian disease, and which appears to be shared by Letterer-Siwe disease.

As to the nature of the predominant cell concerned in these two cases which has thus far been variously termed a mononuclear cell, a histiocyte or a reticulo-endothelial cell, attention has been drawn to its ability to ingest red cells and to store fatty substances and haemosiderin, properties characteristic of macrophages, the phagocytic cells of Aschoff's (1924) reticulo-endothelial system. According to Maximow (1924) the macrophage system of cells consists, in essence, of the phagocytic reticular cells, the free macrophages, and the sinus-lining cells of the lymph nodes and of the spleen. On morphological grounds, using aniline dyes alone, it is not possible in the absence of intracytoplasmic ingested particles to separate the first of these three chief groups of cells of the system from the ' reticulum ' cells, the primitive stem cell defined by Robb-Smith (1938). By the application, however, of silver impregnation techniques developed by Hortega del Rio and de Asúa (1921), and subsequently used extensively by Robb-Smith and by Marshall (1946, 1950), it has been shown by these last two authors that whereas the ' reticulum ' cell is not impregnated, the cells of the macrophage system are intensely blackened. By applying this criterion of argyrophilia in these two cases it was possible to identify the cells concerned as cells of the macrophage system (histiocytes) even where they were showing no phagocytic activity. Furthermore it was apparent that they tended to deviate to a moderate degree from the normal morphology, being rather larger, more irregular and more plump than is generally found, but no great pleomorphism was seen nor was there any evidence to suggest that the proliferation was anything other than a hyperplasia. Moreover, despite the fact that the architecture of the lymph nodes was greatly obscured, the impression was gained that the proliferation was primarily medullary in origin. It might be reasonable, therefore, to enquire whether this acute variety of Hand-Schüller-Christian disease is in any way related to the disease described by Scott and Robb-Smith (1939) and named ' histiocytic medullary reticulosis '. In brief, this is a disorder affecting adults from the third to the seventh decades, and its main features are high fever, moderate lymph node and splenic enlargement, signs of acute haemolytic anaemia, and occasional petechial skin eruptions. The course is rapid and death occurs in a few months after the onset of the symptoms. In the few recorded cases neither bone lesions, exophthalmos nor diabetes insipidus have been observed. From the descriptions given by these authors and from the study of two unpublished cases from the records of this Institute which amply fulfilled the diagnostic criteria of the disease, it is apparent that, histologically, there is an unusually active proliferation of histiocytes in the lymph nodes and spleen, many bizarre forms being present, and especially noteworthy are occasional multinucleate cells resembling Sternberg-Reed giant cells, as the photomicrographs of Scott and Robb-Smith show. Haemorrhages are abundant in the lesions and erythrophagocytosis is a prominent feature, explaining, perhaps, the clinical finding of haemolytic anaemia, as suggested by McGovern, Morrow and Thomson (1951). Although the presence of fat in the lesions is not mentioned by the original authors, a study of our material shows that while many of the histiocytes contained cytoplasmic vacuoles of variable size in paraffin sections, no mature foam cells could be found and the frozen sections made in one case did not reveal any but the scantiest quantity of sudanophil lipoid. No fibrosis was present, as might be expected if this feature is to be regarded as a phenomenon of chronicity, and eosinophil leucocytes were but scanty in the lesions.

It appears, therefore, that histiocytic medullary reticulosis includes a number of features in common with the acute form of Hand-Schüller-Christian disease. Clinically they both run a rapid course, with lymph node and spleen enlargement, fever, and sometimes petechial rashes, while the pathological basis in both is histiocytic proliferation. The differences, however, are more striking. In the first place the age incidences have nothing in common, though in an attempt to relate the conditions more closely this point might conceivably

be used to help explain away other differences such as the absence of readily observable bone changes. Secondly, the atypical nature of the cells and the pronounced tendency towards red cell destruction must both be regarded as fundamentally peculiar to histiocytic medullary reticulosis, stamping its character both pathologically and clinically. While it is possible that there may be some connection aetiologically between the two conditions, the small number of published cases of histiocytic medullary reticulosis and the absence of any cases which could conceivably be considered as transitional between it and Hand-Schüller-Christian disease, together with the differences listed above, bring us to the conclusion that there is at present no justification for relating them except in so far as they are diseases of the same cell system.

On the other hand the mere existence of a histiocytic hyperplasia, as in histiocytic medullary reticulosis, which does not appear to be concerned with lipoid storage and is apparently unrelated to Hand-Schüller-Christian disease, does lend some support to Siwe's conception of the disease bearing his name. Those authors who have accepted the unity of Letterer-Siwe disease and Hand-Schüller-Christian disease, have done so believing that the cases reported in which no lipoid storage was found would have developed this feature if their course had been more protracted. Siwe contends that this need not necessarily be true since some non-lipoid cases have lived considerably longer than others which showed abundant lipoid storage in the lesions. It is obviously very difficult to decide either way in any particular case in the absence of biochemical and histochemical evidence of the metabolic capabilities of the cells concerned, but it is conceivable that some cases of acute histiocytic hyperplasia in infants do not store lipoid because the cells concerned are not functionally capable of doing so. It is suggested therefore that the term ' Letterer-Siwe disease ' be maintained where at necropsy no lipoid changes are to be found in any case of acute histiocytic hyperplasia in infants, while the presence of lipoid with the appropriate characters should require that the term ' acute form of Hand-Schüller-Christian disease ' be used.

Summary

Clinical and pathological details of two cases of Hand-Schüller-Christian disease in infants are described in full and the resemblances to the changes in Letterer-Siwe disease are discussed.

The relationship between these two conditions and histiocytic medullary reticulosis is discussed.

It is concluded that there is some pathological evidence for considering Letterer-Siwe disease as distinct from the acute form of Hand-Schüller-Christian disease.

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PAROXYSMAL TACHYCARDIA IN INFANCY

BY

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Since Bristowe (1887) first described a series of cases of ' recurrent palpitation of extreme rapidity in persons otherwise healthy ', paroxysmal tachycardia in adults has become a well-known condition. In children the condition has been considered rare. Taran and Jennings (1937) in a review of the literature found only 52 cases under the age of 15 from 1892 to 1935, to which Johnson (1940) added 11. Wright (1938) was able to discover two cases out of 60,000 admissions to a children's hospital, and Landtman (1947) five in 5,600 children examined at his heart clinic. Neubauer (1945), one of the few British contributors to the subject, described 11 cases.

In infancy, sporadic cases have appeared from time to time, but the condition was regarded as an extreme rarity until Hubbard (1941) detailed nine cases seen by him in the period of one year and reviewed 19 others in the literature. Since then the condition has been recognized with increasing frequency, and has even been noted before birth (Garvin and Kline, 1947; Stadler, 1948).

A review of those cases that have been published reveals a uniform clinical picture. It is the purpose of this paper to describe this condition and to give a typical example.

Aetiology

Though in older children infections and digitalis poisoning are often associated with paroxysmal tachycardia, in infancy, in the majority of cases, no underlying cause can be found. A congenital defect of the heart, however, is not a rare finding as may be suspected on clinical grounds in the cases of Colegate and McCulloch (1926), Carr and McClure (1931) and as was found on necropsy in the cases of Schuster and Paterson (1924), Werley (1925) and Young (1944). The majority of post-mortem examinations reveal no cardiac abnormality though Shookoff, Litvak and Matusoff (1932) maintain that there is usually underlying myocardial disease.

That acute infections can be associated with paroxysmal tachycardia in infancy is illustrated by the case of Lyon (1937) when it accompanied an attack of streptococcal meningitis, and in Neubauer's (1945) series where it occurred in meningococcal meningitis, pertussis and in an infant probably suffering from scarlet fever. Taran and Jennings (1937) emphasize the importance of measles and whooping cough.

Though the majority of attacks seem to start for no apparent reason, in individual cases certain specific stimuli or infections seem to have been of importance; diarrhoea (O'Flyn, 1925; Farr and Wegman, 1935), smiling or being tickled (Poynton and Wyllie, 1926), a cold (Van Cleve, 1930). Relapses following a first attack seem to be brought on by any stimulus which raises the pulse rate but in infancy particularly by feeding and defaecation.

The Nature of the Abnormal Rhythm

Campbell (1947) has pointed out that there are four varieties of paroxysmal tachycardia; supraventricular auricular and nodal, auricular fibrillation, auricular flutter and ventricular paroxysmal tachycardia. All these varieties have occurred in young children. The great majority of cases, however, are supraventricular in origin as is pointed out by Johnson (1940) in his review, and as is confirmed by those cases published since. Great difficulty occurs in distinguishing between paroxysmal tachycardia in infancy and paroxysmal flutter, since the infant's ventricle seems to be able to respond to a very high rate of stimulus without heart block appearing. A rate of 365 per minute has been recorded by Silverman and Race (1949). The rhythmical variation in the base line of the electrocardiogram is difficult to see. It is suggested by Frisell (1946) that in the newborn infant a rate over 300 per minute is more likely to be due to auricular flutter, and one below 300 to be paroxysmal tachycardia, but there are exceptions to this rule. The majority of cases are therefore designated as supraventricular paroxysmal tachycardia.

Clinical Picture

Whereas in adults and older children the complaint may be no more than a nuisance, in infants

the extreme rapidity of the heart rate leads to progressive heart failure. The infant usually presents as a case of sudden dyspnoea. The respiratory rate may rise to as much as 90 in the minute. Cyanosis, at first slight and easily missed in a poor light, becomes progressively more marked. The lungs are filled with moist râles, the liver and sometimes the spleen enlarge progressively. Associated with this dyspnoea is often some degree of fever, usually not above 102° F., and a leucocytosis of about 20,000 per c.mm. Radiological examination shows patchy opacities throughout the lung fields and usually an enlarged heart. It is not surprising, therefore, that a diagnosis of bronchopneumonia is made, and sufficient attention not paid to the tachycardia, either because the heart sounds may be inaudible due to the lung adventitiae, or because the tachycardia is attributed to infection. This is the common picture in early infancy, and is seen in the cases described by Sargent and Gillespie (1949), Schieve (1949), Silverman and Race (1949), Moore (1948), Mannheimer (1946), Clarke (1935) and O'Flyn (1925). More rarely, the paroxysm appears to be associated with diarrhoea, vomiting and abdominal pain, and an alimentary infection may be suspected. When consciousness is lost, as is sometimes the case, disease of the central nervous system may be suspected, and finally, due to the large heart, congenital idiopathic hypertrophy of the heart may be suspected.

Such dramatic symptoms are not always seen in infancy, and in many of the cases described at least some of the attacks have caused slight or no symptoms at all. Russell and Ellison's (1927) patient had a tachycardia of 240 per minute in the second attack and had no symptoms, but he was aged 15 months. In early infancy in general symptoms appear to be marked.

Treatment

As opposed to experience with older children and adults, physical methods of bringing the attack to an end are very rarely successful. Drug therapy is usually required and the consensus of opinion favours digitalis. Thus, Gibson (1950) found the drug effective in 10 infants out of 12. Hubbard (1941) treated nine infants with digitalis with success. Campbell (1937), Hobbs (1941), Howard (1945), Hedberg (1945), Frisell (1946), Scott and Limper (1946) and Sargent and Gillespie (1949) have all reported success with the same drug. Garvin and Kline (1947) in a newborn infant found that digitalis gave incomplete control but the addition of quinidine was successful. A contra-indication to digitalis in the opinion of Silverman and Werner (1950) is the Wolff-Parkinson-White syndrome, since the depression of the auriculo-ventricular node due to digitalis diverts the cardiac impulse through the aberrant pathways and aggravates the condition, whereas quinidine is successful in controlling the condition and rendering the electrocardiogram normal. Schieve (1949) considered digitalis to be effective in an infant with this syndrome, but since control was not obtained for three days it is possible that the remission was spontaneous. Bloom and Kendig (1946) expressed the opinion that if the physician has courage enough the attack can be left to terminate spontaneously. That this occurs is undoubted, but that it cannot be relied upon with safety is indicated by the fatal termination in some untreated cases (Werley, 1925; Edeiken, 1943; Silverman and Race, 1949). It is generally agreed that digitalis is contra-indicated in attacks of ventricular paroxysmal tachycardia in which quinidine is effective. The dosage of digitalis which has been found effective in infants has varied; Gibson (1950) recommends 50 mg. digitalis followed by 25 mg. four-hourly, and has given up to 300 mg. in an 8 lb. baby. For intravenous and intramuscular use, 'digifoline' (1 ml.=100 mg. of international standard digitalis powder) has commonly been used in a dose of from $\frac{1}{2}$ to 1 ml. repeated at four- to 12-hourly periods. Moore (1948) recommends 0·2 ml. of the tincture per kilogram body weight.

The value of quinidine is disputed. The experience of Garvin and Kline (1947) has already been quoted. Moore (1948) found this drug effective in an infant who had 31 attacks between the eighth day of life and the age of $5\frac{1}{2}$ months after digitalis and mecholyl had become ineffective. A dose of 120 mg. two-hourly by mouth had to be given and eventually raised to 200 mg. Stadler (1948) in a newborn infant with auricular flutter succeeded in reducing the heart rate from 240 to 120 per minute by giving $\frac{1}{4}$ grain four-hourly, but had to abandon the drug because of vomiting. Digitalis was substituted with success. Sargent and Gillespie (1949) found the addition of quinidine, grains 2 three times a day, prevented the recurrence of tachycardia in an infant aged 6 weeks already under the influence of digitalis. Gibson (1950) recommends the drug for prophylactic use. As opposed to these opinions, Limper (1949) had one infant who had 42 attacks in the 68 days he was observed in hospital and in whom both digitalis and quinidine were of no use prophylactically, and Wright (1938), who followed an infant from the

age of 9 months to 8 years, found neither quinidine nor digitalis of any value in prevention.

More recently, certain parasympathomimetic drugs have been used with success. Mecholyl (acetyl-β-methylcholine) introduced by Starr (1933; 1936) was used by Hubbard (1941) in an infant aged 3 weeks, to whom he gave 5 mg. subcutaneously with alarming results. Moore (1948) gave 0·5 mg. subcutaneously to an infant of 45 days which successfully ended the paroxysm, but also led to such alarming side-effects that atropine had to be given. Following a relapse at the age of 12 weeks, 0·25 mg., 0·5 mg. and 1·5 mg. were given without effect at 30-minute intervals, but after 2 mg. were given the attack was controlled; the side-effects, however, were so marked that it was thought the baby might die. They were again brought to an end with atropine. Brownlee, Waters and McClendon (1950) found in an infant aged 10 weeks that 1 mg. repeated once subcutaneously was effective. Certainly, if this drug is to be used, atropine must be available to control its effects; it should never be given intravenously. Less violent in effect, but acting in a similar manner, is acetylcholine which Philipsborn and Gibson (1948) found effective when given intravenously in a dose varying from 1 to 4 mg. Cunningham and Schnitzker (1950) gave 0·2 mg. intravenously to a child of 9 months and successfully ended the paroxysm. Landtman (1947) found prostigmine $\frac{1}{8}$ mg. effective in five infants, and Mannheimer (1946) neostigmine $\frac{1}{8}$ mg. subcutaneously in an infant aged 3 weeks.

Recently, neosynephrine (laevo-α-hydroxy-β-methyl amino-3-hydroxy-ethylbenzene hydrochloride) has been used in adults (Youmans, Goodman and Gould, 1947), and in a child aged 27 months by Cunningham and Snitzker (1950) who recommend giving 0·1 mg. intravenously and increasing by 0·1 mg. each 30 minutes up to a dose of 0·5 mg. The drug acts by causing a sudden rise in blood pressure, but no reference to its use in infants has been found.

Prognosis

The Individual Attack. This is more serious in an infant than in an older child or adult, but as in the latter, depends mainly on the presence of underlying cardiac disease.

Future Attacks. Though many infants have recurrent attacks, there is in infants a greater likelihood of the attacks ceasing completely than in older children or adults.

Case Report

P.B., the fourth child of a healthy family, was born at home, weighing 8 lb. The delivery was normal and the mother had been well during her pregnancy save for pyelitis in the early months. For the first 24 hours the baby was noticed to be blue and no attempt was made at feeding. On the second day of life he seemed well, but from the third day he suffered from recurring attacks of blueness which appeared to be precipitated by feeding or straining at stool. These attacks lasted about five minutes and were associated with dyspnoea and gasping respirations. He was first seen on the eleventh day of

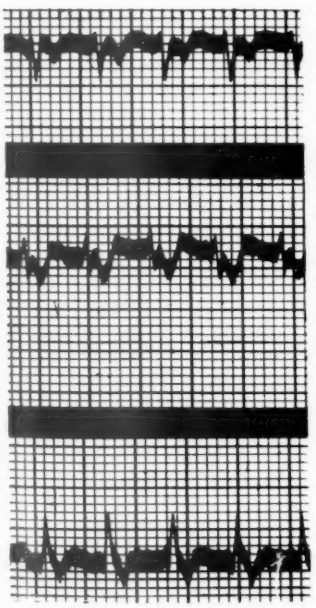

FIG. 1

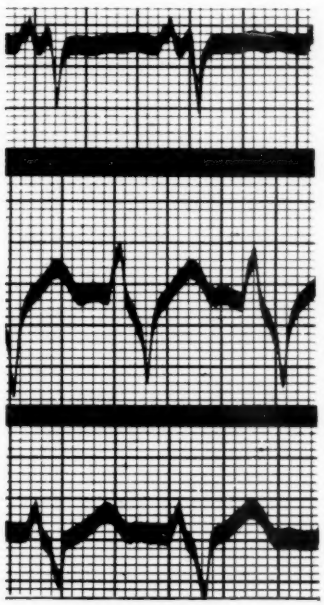

FIG. 2

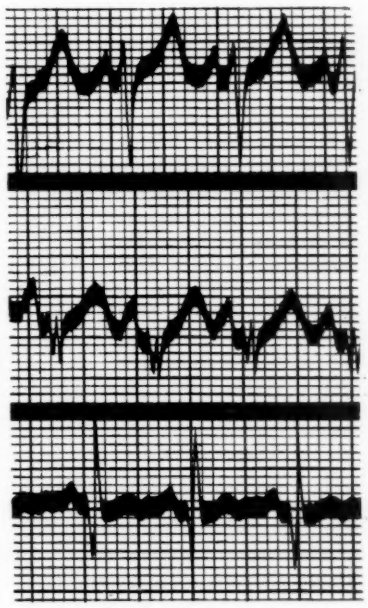

FIG. 3

life. Gross dyspnoea was present, the respiratory rate being 90 per minute, and there was slight cyanosis of the lips. He was afebrile, and the pulse rate counted with the stethoscope was 240 per minute. It was difficult to be certain of the latter as there were profuse moist sounds throughout the lung fields which tended to obscure the heart sounds. The heart was enlarged, the apex beat being in the anterior axillary line. The liver was enlarged down to the umbilicus, and there was pitting oedema of both legs. A provisional diagnosis of paroxysmal tachycardia was made, and he was admitted to hospital where an electrocardiogram was taken (Fig. 1). 'Digoxin', 0·125 mg., was given immediately by mouth. Six hours later the heart rate had fallen to 140 per minute and never rose above 150 per minute again. Digoxin was continued in a dose of 0·025 mg. eight-hourly for 48 hours, then 12-hourly for another 48 hours. An electrocardiogram taken 48 hours after the beginning of treatment (thirteenth day of life) showed the heart rate to be 120 per minute with evidence of the effect of digitalis (Fig. 2), and the record was essentially similar 48 hours later. Within 24 hours of the beginning of treatment the respiratory rate had fallen to 65 per minute, slight enlargement of the liver was still present and oedema of the legs still detectable. Within 48 hours no enlargement of the heart could be noted, and all abnormal signs had disappeared. The respiratory rate was elevated for five more days and then fell to a normal figure. On the second day of treatment, while the oedema was diminishing, looseness and frequency of stools occurred. At no time was a cardiac murmur noted, and on the fifty-eighth day of life an electrocardiogram revealed a normal record for his age (Fig. 3). At the age of 9 months he had developed normally and had had no further attacks of paroxysmal tachycardia, and no abnormalities could be detected clinically.

Summary

A case of paroxysmal tachycardia in infancy is described and the incidence, aetiology, treatment and prognosis discussed with reference to previous cases described in the literature.

I should like to thank Dr. E. M. Davies for letting me see the patient, and Dr. R. W. Brookfield for advice in preparing this paper.

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THE RESTORATION OF NORMAL BREATHING IN ASTHMATIC CHILDREN

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This preliminary report records a clinical study of the relation between the bony framework of the skull and respiratory function conducted at the Royal Chest Hospital over a period of five years. The purpose is to present a new angle of approach to the problem of asthma in childhood.

Most of the commonly accepted methods of treatment aim at the correction of an allergic diathesis, organic disease in the upper respiratory tract, infection or a psychological state. These methods may be successful, but it is well known that the asthma may recur. A successful result of the course of treatment outlined in this paper causes a restoration to normal of a previously abnormal upper respiratory tract by altering anatomical relations. This accomplished, there would seem to be a much greater chance that the improvement produced in the mechanics of breathing will prove to be permanent.

In a high percentage of asthmatic children there is a malformation of the bony framework of the face which has proved capable of being corrected without surgical intervention, and therefore this investigation was approached from the aspect of considering to what extent the various types of facial and other skeletal deformity characteristic of the asthmatic may be an aetiological factor in the disease and its associated abnormal posture.

Normal posture is a physiological expression of a balanced mechanism manifested in rhythmic movement and static poise, whether it concerns the entire organism or a particular component. The postural adjustments characteristic of the asthmatic during phases of activity and rest represent an effort at accommodation towards adequate respiratory function by an organism in a state of imbalance. Structure and function being interdependent, it is reasonable to postulate that an inherent structural fault, which might impose a need for postural accommodation, could be an important feature in the production of the asthmatic habitus. It is also probable that the relatively greater expenditure of neuromuscular energy required by an ill-balanced organism to maintain asymmetric postural positions, even during rest, tends not only to maintain but to accentuate a vicious circle.

The writer, while engaged upon another clinical investigation, observed that children with underdeveloped and malrelated jaws have not only facial asymmetry, but also tend to develop a stooping posture, winged scapulae and a liability to post-nasal catarrh and other respiratory symptoms (Nove, 1945).

It became apparent from a close study of the mechanism of mastication, deglutition and respiration in a number of children presenting a variety of the malformations that the action of the muscles of the face and neck lacked the synergy of action to be seen in those whose skeletal and muscular formation were properly balanced. It was also found that this lack of harmony could be reduced by employing orthopaedic methods.

The mechanism employed was introduced originally as an orthodontic appliance by Robin (1929) and further developed by Andresen (1938). Its application and construction, however, were adapted by the writer to the orthopaedic requirements of correcting a faulty integration of the structures which comprise the cervico-facial component (Nove, 1946a). The object is to correct the abnormality of the bony framework of the face and thus to improve the mechanism of respiration. In time it is found that a more normal airway is the result. For this purpose the maxilla is regarded as the proximal end and the mandible the distal end of the component.

It is expedient to begin the first stage of the orthopaedic procedure extra-orally. Plaster casts are obtained in the ordinary way, care being taken to ensure that they are sharply defined and extend beyond the junction of the hard and soft palate and tuberosities in the upper jaw, and that the lower cast is deep enough to include the sites of the

mylohyoid ridges and geniohyoid tubercle. These anatomical constants are readily discernible on the casts and are important landmarks which guide the clinician in plotting out a mandibular base line from which to determine the correct vertical and antero-posterior relationship of the jaws (Nove, 1946b). This aspect of the procedure has been discussed by Campbell (1950).

A roll of soft wax is placed between the ' occlusal ' surfaces of the teeth of the upper and lower models which are then manoeuvred until a correct inter-maxillary relationship appears to have been found. This provisional wax ' block ' is then placed on the occlusal surface of the lower jaw, which is guided to the upper jaw so that the teeth bite into the corresponding facets made in the wax, and the patient is instructed to close the mouth; an intra-oral splint is now fashioned in a plastic material. The details of the mechanical procedure are outside the scope of this report. The purpose of the splint is to retain the new inter-maxillary relationship intermittently, specially during the night.

When a splint made to a correctly plotted orientation is placed in the mouth, certain characteristic behaviour patterns of the structures concerned occur as the splint engages both jaws. The orbicularis oris closes, initiating an act of swallowing which, in the normal, has a functional pattern of its own (Nove, 1948), and is identified by a synchronized movement in the angle of the jaw and neck as the thyroid prominence is seen to trace the excursion made by the tongue and associated structures in an upward and slightly forward direction, registering a vigorous synergic contraction of the facial and neck muscles, ending in relaxation.

The synergy of muscular action exhibited during this process and the fact that it is followed by an expression of greater repose, suggestive of a state of physiological rest, indicate that the bony framework of the face has been adequately augmented and the requisite fulcrum for full muscular action provided, thereby reducing faulty integration in the internal and external structures of the face and neck. An alteration in cranio-cervical posture takes place and an appreciable improvement in nasal breathing and costo-diaphragmatic rhythm follows immediately. Sometimes the change is dramatic, but generally it fluctuates to some extent before normal breathing is restored.

Provided that the patient can co-operate fully and that the clinician is meticulously careful in maintaining the requisite structural balance, smooth respiratory excursion ensues, symptoms gradually disappear and, in due course, normal health is established. At the same time the interaction imposed by the newly introduced balanced muscular stresses has the corresponding effect of remoulding the bony framework of the face, including the temporo-mandibular joints, in accordance with accepted principles of bone reconstruction known since the days of John Hunter and fully discussed by Brailsford (1945). Sicher (1947) treats of the special characteristic features concerning the growth and development of the bony elements of the structures under discussion.

The length of time required for reconstruction from a faulty structure of the face to one that is so balanced as to restore normal breathing varies with the age of the patient at the beginning of treatment and the degree of structural fault. If treatment begins at 3 years of age or earlier the minimum period required is, on an average, three years. Similarly, children with mixed dentition and adolescents require on an average between four and five years to restore the normal structure. That is to say, although improved respiratory function follows shortly after the patient begins to wear the splint, unaided normal breathing cannot be assured until the bony framework of the face has been adequately reshaped, establishing a harmonious interplay between the internal and external structures of the head and neck component. Only then can the splint be discarded.

In the course of the treatment frequent adjustments to the splint, as well as new orientations and new splints, have to be made to meet the constant changes of growth and development in order to maintain and eventually consolidate the improved structural balance and cranio-cervical and general posture.

To maintain this biological process constant supervision is required. The balance of this equilibrium is a very delicate one; for example, the cusp or incisal edge of an erupting permanent tooth impinging on the splint produces a ' high spot ' (with or without pain) and can disturb the equilibrium sufficiently to reverse an otherwise favourable clinical course, for when the bony fulcrum is even slightly upset functional imbalance is reintroduced.

The facial skeleton, no less than other bones, provides a fulcrum for muscular contractions and support during physiological rest. If the fulcrum is out of true because of faulty skeletal formation, function is forced into a variety of patterns of adaptive forms (Nove, 1948). Intra-oral splints made to correct anatomical faults have, therefore, to be renewed every few months as well as frequently adjusted, in order to keep in step with the

process of growth and development, as well as to maintain the required equilibrium for normal muscular activity, until the bony support has been helped by the interaction between structure and function sufficiently to reach that maximum reconstruction at which the correct functional interplay will maintain the required balance.

Clinical Data

This study concerns a group of 74 asthmatic children between the ages of 3 and 16. (The average age at the beginning of treatment was 9 years.) The cases were selected from patients attending the Clinic between December, 1943, and November, 1948, as suitable for treatment because most had proved resistant to the usual methods and thereby provided a form of control, and, in addition, their attendance had been fairly regular. In each case the presenting symptom was asthma.

In order not to invalidate the scientific value of the conclusions to be derived from the method of treatment described, patients (or parents) were also instructed to discontinue other remedies and to get in touch with the hospital or their doctor should they have an acute attack of asthma. Also, whenever possible, the family doctor was asked to refrain from prescribing and to render only such aid as an emergency might necessitate.

A full clinical and pathological examination was carried out in each case before the patient was accepted as being suitable for treatment. The general outline of the investigation followed that in routine use in the Asthma Clinic at the Royal Chest Hospital and described elsewhere by Maxwell (1936). Analysis of the factors present showed results which were comparable with those reported in other series.

Allergy. In every case the history, family history, and the results of skin tests were taken into consideration. An allergic factor was considered to be present in 44 of the cases.

The Upper Respiratory Tract. The nose and throat were examined by routine methods, including radiography in doubtful cases. Various abnormalities, such as 'collapsed' nares, faulty nasal airway, mouth breathing, infected sinuses, clinically infected tonsils, granular mucosa, or ear discharge, were reported in 49 cases.

The Lower Respiratory Tract. Bronchitis, emphysema and a mild degree of bronchiectasis were the commonest abnormalities discovered, and in addition, there was a considerable chest deformity in a number of patients. In all, it was considered that the bronchopulmonary system showed evidence of organic change in 26 cases.

The Psychological Factor. This is the most difficult of all factors to assess in asthmatic children, for it is hard to know how much of the nervous symptoms is a part of the child's constitution and how much has been produced by previous attempts at medical or surgical treatment. In addition, it is not always possible to assess fully the patient's background, and yet it is well recognized that an unsatisfactory home environment is a very common cause of the persistence of symptoms. From information obtained from parents and other sources, there appeared to be a significant psychological abnormality in 30 of these cases.

During the first five years of this investigation the routine examination and clinical assessment were carried out by the writer jointly with Dr. Beryl Barsby, formerly Registrar at the Royal Chest Hospital. The final clinical assessment and classification of every case was carried out by Dr. James Maxwell.

Results

It is never easy to present the results of treatment in asthma, for the multiplicity of factors concerned make it difficult to form a balanced judgment on the effect of a particular remedy. The only possible criterion is the cessation of attacks of asthma, and, therefore, cases have been divided into three groups.

Group 1 (34 Cases). The patients in this group have all been completely free from asthma for at least one year and many for longer periods. They are all engaged in full-time school activities and they are capable of taking part in the usual sports and games without restriction.

Group 2 (20 Cases). In this group the result is not quite so satisfactory, although every child is leading a normal life. There is no significant interference with attendance at school, but there are occasional attacks of asthma and full physical exercise is not achieved.

Group 3 (20 Cases). No significant improvement is seen in this group.

There was a significantly constant rise in the curve of the vital capacity graph in most of the cases under treatment, and radiographic evidence of favourable bony changes in the thoracic cage, as well as in the facial bones, supporting the subjective evidence. A point of interest was that neither the allergic nor the psychological factor appeared to influence the clinical course of the series of cases under review.

A favourable prognosis seems to be dependent on (1) full co-operation on the part of the patient; (2) successful reduction of structural imbalance; (3) avoidance of expenditure of energy beyond the

patient's physical capacity in the early phases of treatment. As a result of the feeling of relief experienced, the patient tends, understandably, to overstep the respiratory threshold reached. Failure to exercise restraint may in some cases interfere with a favourable clinical course; (4) an adequate length of time is required for treatment, because the structural changes which permanently establish normal respiratory function are inevitably gradual and individually variable.

Summary and Conclusions

A group of 74 children was studied in which the presenting symptom was asthma; all of them showed some form of faulty jaw formation. Symptoms did not appear to relate to any particular type of deformity, and the type generally referred to as adenoid facies appeared to respond to the treatment as readily as other types.

The clinical findings were made under conditions approaching control and suggest that the orthopaedic method evolved offers a means whereby normal respiratory function may be restored in asthmatic children whilst resolving at the same time a structural fault which may be the causative factor. The method is also of value in clinical research.

I am most grateful to Dr. James Maxwell for the opportunity to develop the investigation and for very generous guidance throughout; to Dr. Beryl Barsby, who meticulously compiled and collated much clinical data; and to Mr. Ian Robin for his evaluation of some of the cases.

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